

**CENTER FOR DRUG EVALUATION AND
RESEARCH**

APPLICATION NUMBER:

202067Orig1s000

ADMINISTRATIVE and CORRESPONDENCE
DOCUMENTS

EXCLUSIVITY SUMMARY

NDA # **202067**

SUPPL #

HFD # **120**

Trade Name **Onfi**

Generic Name **clobazam**

Applicant Name **Lundbeck Inc.**

Approval Date, If Known **October 21, 2011**

PART I IS AN EXCLUSIVITY DETERMINATION NEEDED?

1. An exclusivity determination will be made for all original applications, and all efficacy supplements. Complete PARTS II and III of this Exclusivity Summary only if you answer "yes" to one or more of the following questions about the submission.

a) Is it a 505(b)(1), 505(b)(2) or efficacy supplement?

YES NO

If yes, what type? Specify 505(b)(1), 505(b)(2), SE1, SE2, SE3,SE4, SE5, SE6, SE7, SE8

505(b)(1) NDA

c) Did it require the review of clinical data other than to support a safety claim or change in labeling related to safety? (If it required review only of bioavailability or bioequivalence data, answer "no.")

YES NO

If your answer is "no" because you believe the study is a bioavailability study and, therefore, not eligible for exclusivity, EXPLAIN why it is a bioavailability study, including your reasons for disagreeing with any arguments made by the applicant that the study was not simply a bioavailability study.

If it is a supplement requiring the review of clinical data but it is not an effectiveness supplement, describe the change or claim that is supported by the clinical data:

d) Did the applicant request exclusivity?

YES NO

If the answer to (d) is "yes," how many years of exclusivity did the applicant request?

5 years; indication also has orphan designation

e) Has pediatric exclusivity been granted for this Active Moiety?

YES

NO

If the answer to the above question in YES, is this approval a result of the studies submitted in response to the Pediatric Written Request?

IF YOU HAVE ANSWERED "NO" TO ALL OF THE ABOVE QUESTIONS, GO DIRECTLY TO THE SIGNATURE BLOCKS AT THE END OF THIS DOCUMENT.

2. Is this drug product or indication a DESI upgrade?

YES

NO

IF THE ANSWER TO QUESTION 2 IS "YES," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8 (even if a study was required for the upgrade).

PART II FIVE-YEAR EXCLUSIVITY FOR NEW CHEMICAL ENTITIES

(Answer either #1 or #2 as appropriate)

1. Single active ingredient product.

Has FDA previously approved under section 505 of the Act any drug product containing the same active moiety as the drug under consideration? Answer "yes" if the active moiety (including other esterified forms, salts, complexes, chelates or clathrates) has been previously approved, but this particular form of the active moiety, e.g., this particular ester or salt (including salts with hydrogen or coordination bonding) or other non-covalent derivative (such as a complex, chelate, or clathrate) has not been approved. Answer "no" if the compound requires metabolic conversion (other than deesterification of an esterified form of the drug) to produce an already approved active moiety.

YES

NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

2. Combination product.

If the product contains more than one active moiety(as defined in Part II, #1), has FDA previously approved an application under section 505 containing any one of the active moieties in the drug product? If, for example, the combination contains one never-before-approved active moiety and one previously approved active moiety, answer "yes." (An active moiety that is marketed under an OTC monograph, but that was never approved under an NDA, is considered not previously approved.)

YES NO

If "yes," identify the approved drug product(s) containing the active moiety, and, if known, the NDA #(s).

NDA#

NDA#

NDA#

IF THE ANSWER TO QUESTION 1 OR 2 UNDER PART II IS "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8. (Caution: The questions in part II of the summary should only be answered "NO" for original approvals of new molecular entities.)

IF "YES," GO TO PART III.

PART III THREE-YEAR EXCLUSIVITY FOR NDAs AND SUPPLEMENTS

To qualify for three years of exclusivity, an application or supplement must contain "reports of new clinical investigations (other than bioavailability studies) essential to the approval of the application and conducted or sponsored by the applicant." This section should be completed only if the answer to PART II, Question 1 or 2 was "yes."

1. Does the application contain reports of clinical investigations? (The Agency interprets "clinical investigations" to mean investigations conducted on humans other than bioavailability studies.) If the application contains clinical investigations only by virtue of a right of reference to clinical investigations in another application, answer "yes," then skip to question 3(a). If the answer to 3(a) is "yes" for any investigation referred to in another application, do not complete remainder of summary for that investigation.

YES NO

IF "NO," GO DIRECTLY TO THE SIGNATURE BLOCKS ON PAGE 8.

2. A clinical investigation is "essential to the approval" if the Agency could not have approved the application or supplement without relying on that investigation. Thus, the investigation is not essential to the approval if 1) no clinical investigation is necessary to support the supplement or application in light of previously approved applications (i.e., information other than clinical trials, such as bioavailability data, would be sufficient to provide a basis for approval as an ANDA or 505(b)(2) application because of what is already known about a previously approved product), or 2) there are published reports of studies (other than those conducted or sponsored by the applicant) or other publicly available data that independently would have been sufficient to support approval of the application, without reference to the clinical investigation submitted in the application.

(a) In light of previously approved applications, is a clinical investigation (either conducted by the applicant or available from some other source, including the published literature) necessary to support approval of the application or supplement?

YES NO

If "no," state the basis for your conclusion that a clinical trial is not necessary for approval AND GO DIRECTLY TO SIGNATURE BLOCK ON PAGE 8:

(b) Did the applicant submit a list of published studies relevant to the safety and effectiveness of this drug product and a statement that the publicly available data would not independently support approval of the application?

YES NO

(1) If the answer to 2(b) is "yes," do you personally know of any reason to disagree with the applicant's conclusion? If not applicable, answer NO.

YES NO

If yes, explain:

(2) If the answer to 2(b) is "no," are you aware of published studies not conducted or sponsored by the applicant or other publicly available data that could independently demonstrate the safety and effectiveness of this drug product?

YES NO

If yes, explain:

(c) If the answers to (b)(1) and (b)(2) were both "no," identify the clinical investigations submitted in the application that are essential to the approval:

Studies comparing two products with the same ingredient(s) are considered to be bioavailability studies for the purpose of this section.

3. In addition to being essential, investigations must be "new" to support exclusivity. The agency interprets "new clinical investigation" to mean an investigation that 1) has not been relied on by the agency to demonstrate the effectiveness of a previously approved drug for any indication and 2) does not duplicate the results of another investigation that was relied on by the agency to demonstrate the effectiveness of a previously approved drug product, i.e., does not redemonstrate something the agency considers to have been demonstrated in an already approved application.

a) For each investigation identified as "essential to the approval," has the investigation been relied on by the agency to demonstrate the effectiveness of a previously approved drug product? (If the investigation was relied on only to support the safety of a previously approved drug, answer "no.")

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigations, identify each such investigation and the NDA in which each was relied upon:

b) For each investigation identified as "essential to the approval", does the investigation duplicate the results of another investigation that was relied on by the agency to support the effectiveness of a previously approved drug product?

Investigation #1 YES NO

Investigation #2 YES NO

If you have answered "yes" for one or more investigation, identify the NDA in which a similar investigation was relied on:

c) If the answers to 3(a) and 3(b) are no, identify each "new" investigation in the application or supplement that is essential to the approval (i.e., the investigations listed in #2(c), less any that are not "new"):

(c) Notwithstanding an answer of "yes" to (a) or (b), are there other reasons to believe that the applicant should not be credited with having "conducted or sponsored" the study? (Purchased studies may not be used as the basis for exclusivity. However, if all rights to the drug are purchased (not just studies on the drug), the applicant may be considered to have sponsored or conducted the studies sponsored or conducted by its predecessor in interest.)

YES NO

If yes, explain:

=====

Name of person completing form: **Su-Lin Sun, PharmD**

Title: **Regulatory Project Manager**

Date: **October 21, 2011**

Name of Office/Division Director signing form: **Ellis F. Unger, M.D.**

Title: **Deputy Director, Office of Drug Evaluation I**

Form OGD-011347; Revised 05/10/2004; formatted 2/15/05

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SU-LIN SUN
10/21/2011

ELLIS F UNGER
10/21/2011

PEDIATRIC PAGE

(Complete for all filed original applications and efficacy supplements)

JA/BLA#: **202067** Supplement Number: **N/A** NDA Supplement Type: **1 (NME)**
Division Name: **Neurology** PDUFA Goal Date: Stamp Date: **12/23/2010**
Products **10/23/2011**

Proprietary Name: **Onfi**
Established/Generic Name: **clobazam**
Dosage Form: **5mg, 10mg, and 20mg tablets**
Applicant/Sponsor: **Lundbeck**

Indication(s) previously approved (please complete this question for supplements and Type 6 NDAs only):
N/A

Pediatric use for each pediatric subpopulation must be addressed for each indication covered by current application under review. A Pediatric Page must be completed for each indication.

Number of indications for this pending application(s): **1**
(Attach a completed Pediatric Page for each indication in current application.)

Indication: Adunctive therapy for the treatment of seizures associated with Lennox-Gastaut Syndrome (LGS) in patients 2 years of age or older

Q1: Is this application in response to a PREA PMR? Yes Continue
No Please proceed to Question 2.

If Yes, NDA/BLA#: _____ Supplement #: _____ PMR #: _____

Does the division agree that this is a complete response to the PMR?

- Yes. Please proceed to Section D.
 No. Please proceed to Question 2 and complete the Pediatric Page, as applicable.

Q2: Does this application provide for (If yes, please check all categories that apply and proceed to the next question):

(a) NEW active ingredient(s) (includes new combination); indication(s); dosage form; dosing regimen; or route of administration?*

(b) No. PREA does not apply. **Skip to signature block.**

* **Note for CDER: SE5, SE6, and SE7 submissions may also trigger PREA.**

Q3: Does this indication have orphan designation?

- Yes. PREA does not apply. **Skip to signature block.**
 No. Please proceed to the next question.

Q4: Is there a full waiver for all pediatric age groups for this indication (check one)?

- Yes: (Complete Section A.)
 No: Please check all that apply:
 Partial Waiver for selected pediatric subpopulations (Complete Sections B)
 Deferred for some or all pediatric subpopulations (Complete Sections C)
 Completed for some or all pediatric subpopulations (Complete Sections D)
 Appropriately Labeled for some or all pediatric subpopulations (Complete Sections E)
 Extrapolation in One or More Pediatric Age Groups (Complete Section F)
(Please note that Section F may be used alone or in addition to Sections C, D, and/or E.)

Section A: Fully Waived Studies (for all pediatric age groups)

Reason(s) for full waiver: (**check, and attach a brief justification for the reason(s) selected**)

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____
- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients AND is not likely to be used in a substantial number of pediatric patients.
- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are fully waived on this ground, this information must be included in the labeling.*)

Justification attached.

If studies are fully waived, then pediatric information is complete for this indication. If there is another indication, please complete another Pediatric Page for each indication. Otherwise, this Pediatric Page is complete and should be signed.

Section B: Partially Waived Studies (for selected pediatric subpopulations)

Check subpopulation(s) and reason for which studies are being partially waived (fill in applicable criteria below):

Note: If Neonate includes premature infants, list minimum and maximum age in "gestational age" (in weeks).

		Reason (see below for further detail):					
		minimum	maximum	Not feasible [#]	Not meaningful therapeutic benefit*	Ineffective or unsafe [†]	Formulation failed ^Δ
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Reason(s) for partial waiver (**check reason** corresponding to the category checked above, and **attach a brief justification**):

Not feasible:

- Necessary studies would be impossible or highly impracticable because:
 - Disease/condition does not exist in children
 - Too few children with disease/condition to study
 - Other (e.g., patients geographically dispersed): _____

Not meaningful therapeutic benefit:

- Product does not represent a meaningful therapeutic benefit over existing therapies for pediatric patients in this/these pediatric subpopulation(s) AND is not likely to be used in a substantial number of pediatric patients in this/these pediatric subpopulation(s).

† Ineffective or unsafe:

- Evidence strongly suggests that product would be unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)
- Evidence strongly suggests that product would be ineffective and unsafe in all pediatric subpopulations (*Note: if studies are partially waived on this ground, this information must be included in the labeling.*)

Δ Formulation failed:

- Applicant can demonstrate that reasonable attempts to produce a pediatric formulation necessary for this/these pediatric subpopulation(s) have failed. (*Note: A partial waiver on this ground may only cover the pediatric subpopulation(s) requiring that formulation. An applicant seeking a partial waiver on this ground must submit documentation detailing why a pediatric formulation cannot be developed. This submission will be posted on FDA's website if waiver is granted.*)

- Justification attached.

For those pediatric subpopulations for which studies have not been waived, there must be (1) corresponding study plans that have been deferred (if so, proceed to Sections C and complete the PeRC Pediatric Plan Template); (2) submitted studies that have been completed (if so, proceed to Section D and complete the PeRC Pediatric Assessment form); (3) additional studies in other age groups that are not needed because the drug is appropriately labeled in one or more pediatric subpopulations (if so, proceed to Section E); and/or (4) additional studies in other age groups that are not needed because efficacy is being extrapolated (if so, proceed to Section F). Note that more than one of these options may apply for this indication to cover all of the pediatric subpopulations.

Section C: Deferred Studies (for selected pediatric subpopulations).

Check pediatric subpopulation(s) for which pediatric studies are being deferred (and fill in applicable reason below):

Deferrals (for each or all age groups):			Reason for Deferral			Applicant Certification †
			Ready for Approval in Adults	Need Additional Adult Safety or Efficacy Data	Other Appropriate Reason (specify below)*	Received
Population	minimum	maximum				
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> All Pediatric Populations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>	<input type="checkbox"/>
Date studies are due (mm/dd/yy): _____						

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

* Other Reason: _____

IF THERE ARE QUESTIONS, PLEASE CONTACT THE CDER PMHS VIA EMAIL (cderpms@fda.hhs.gov) OR AT 301-796-0700.

Note: Studies may only be deferred if an applicant submits a certification of grounds for deferring the studies, a description of the planned or ongoing studies, evidence that the studies are being conducted or will be conducted with due diligence and at the earliest possible time, and a timeline for the completion of the studies. If studies are deferred, on an annual basis applicant must submit information detailing the progress made in conducting the studies or, if no progress has been made, evidence and documentation that such studies will be conducted with due diligence and at the earliest possible time. This requirement should be communicated to the applicant in an appropriate manner (e.g., in an approval letter that specifies a required study as a post-marketing commitment.)

If all of the pediatric subpopulations have been covered through partial waivers and deferrals, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section D: Completed Studies (for some or all pediatric subpopulations).

Pediatric subpopulation(s) in which studies have been completed (check below):

Population		minimum	maximum	PeRC Pediatric Assessment form attached?.	
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	Yes <input type="checkbox"/>	No <input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If there are no further pediatric subpopulations to cover based on partial waivers, deferrals and/or completed studies, Pediatric Page is complete and should be signed. If not, complete the rest of the Pediatric Page as applicable.

Section E: Drug Appropriately Labeled (for some or all pediatric subpopulations):

Additional pediatric studies are not necessary in the following pediatric subpopulation(s) because product is appropriately labeled for the indication being reviewed:

Population		minimum	maximum
<input type="checkbox"/>	Neonate	__ wk. __ mo.	__ wk. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	Other	__ yr. __ mo.	__ yr. __ mo.
<input type="checkbox"/>	All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

If all pediatric subpopulations have been covered based on partial waivers, deferrals, completed studies, and/or

Section F: Extrapolation from Other Adult and/or Pediatric Studies (for deferred and/or completed studies)

Note: Pediatric efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations if (and only if) (1) the course of the disease/condition AND (2) the effects of the product are sufficiently similar between the reference population and the pediatric subpopulation for which information will be extrapolated. Extrapolation of efficacy from studies in adults and/or other children usually requires supplementation with other information obtained from the target pediatric subpopulation, such as pharmacokinetic and safety studies. Under the statute, safety cannot be extrapolated.

Pediatric studies are not necessary in the following pediatric subpopulation(s) because efficacy can be extrapolated from adequate and well-controlled studies in adults and/or other pediatric subpopulations:

Population	minimum	maximum	Extrapolated from:	
			Adult Studies?	Other Pediatric Studies?
<input type="checkbox"/> Neonate	__ wk. __ mo.	__ wk. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input type="checkbox"/> Other	__ yr. __ mo.	__ yr. __ mo.	<input type="checkbox"/>	<input type="checkbox"/>
<input checked="" type="checkbox"/> All Pediatric Subpopulations	0 yr. 0 mo.	16 yr. 11 mo.	<input type="checkbox"/>	<input type="checkbox"/>

Are the indicated age ranges (above) based on weight (kg)? No; Yes.

Are the indicated age ranges (above) based on Tanner Stage? No; Yes.

Note: If extrapolating data from either adult or pediatric studies, a description of the scientific data supporting the extrapolation must be included in any pertinent reviews for the application.

If there are additional indications, please complete the attachment for each one of those indications. Otherwise, this Pediatric Page is complete and should be signed and entered into DFS or DARRTS as appropriate after clearance by PeRC.

This page was completed by:

 10/06/2011 (OK by GGI, PE2C on 10/6/11)
Su-Lin Sun, Pharm D, Regulatory Project Manager

Debarment Certification

Title: Debarment Certification
Product Name: Clobazam
Formulation: Tablet
Indication: Lennox-Gastaut Syndrome
Sponsor: Lundbeck Inc.
4 Parkway North, Suite 200
Deerfield, IL 60015
Date: 15 September 2010

Confidentiality Statement

The information contained herein is confidential and the proprietary property of Lundbeck Inc. and its parent and affiliates; and any unauthorized use or disclosure of such information without the prior written authorization of Lundbeck Inc. and its parent and affiliates is expressly prohibited.

Lundbeck Inc. certifies that it is not debarred, and did not and will not use in any capacity the services of any person or company debarred under Section 306(k)(1) of the Federal Food, Drug, and Cosmetic Act in connection with this application.



Jeanine M. Swalec

Sr. Director, Global Regulatory Affairs
Lundbeck Inc.

ACTION PACKAGE CHECKLIST

APPLICATION INFORMATION¹

NDA # 202067 BLA #	NDA Supplement # BLA STN #	If NDA, Efficacy Supplement Type:
Proprietary Name: Onfi Established/Proper Name: clobazam Dosage Form: 5mg, 10mg and 20mg		Applicant: Agent for Applicant (if applicable):
RPM: Su-Lin Sun, PharmD		Division: Neurology Products
<p>NDA: NDA Application Type: <input checked="" type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2) Efficacy Supplement: <input type="checkbox"/> 505(b)(1) <input type="checkbox"/> 505(b)(2)</p> <p>(A supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2). Consult page 1 of the 505(b)(2) Assessment or the Appendix to this Action Package Checklist.)</p>		<p>505(b)(2) Original NDAs and 505(b)(2) NDA supplements: Listed drug(s) relied upon for approval (include NDA #(s) and drug name(s):</p> <p>Provide a brief explanation of how this product is different from the listed drug.</p> <p>If no listed drug, explain.</p> <p><input type="checkbox"/> This application relies on literature. <input type="checkbox"/> This application relies on a final OTC monograph. <input type="checkbox"/> Other (explain)</p> <p><u>Two months prior to each action, review the information in the 505(b)(2) Assessment and submit the draft to CDER OND IO for clearance. Finalize the 505(b)(2) Assessment at the time of the approval action.</u></p> <p><u>On the day of approval, check the Orange Book again for any new patents or pediatric exclusivity.</u></p> <p><input type="checkbox"/> No changes <input type="checkbox"/> Updated Date of check:</p> <p>If pediatric exclusivity has been granted or the pediatric information in the labeling of the listed drug changed, determine whether pediatric information needs to be added to or deleted from the labeling of this drug.</p>
❖ Actions		
<ul style="list-style-type: none"> • Proposed action on 10/21/2011 • User Fee Goal Date is <u>10/23/2011</u> • Previous actions (<i>specify type and date for each action taken</i>) 		<input checked="" type="checkbox"/> AP <input type="checkbox"/> TA <input type="checkbox"/> CR <input checked="" type="checkbox"/> None
❖ If accelerated approval or approval based on efficacy studies in animals, were promotional materials received? Note: Promotional materials to be used within 120 days after approval must have been submitted (for exceptions, see http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/ucm069965.pdf). If not submitted, explain		<input type="checkbox"/> Received

¹ The **Application Information** section is (only) a checklist. The **Contents of Action Package** section (beginning on page 5) lists the documents to be included in the Action Package.

Application Characteristics ²			
<p>Review priority: <input checked="" type="checkbox"/> Standard <input type="checkbox"/> Priority Chemical classification (new NDAs only):</p> <table style="width: 100%; border: none;"> <tr> <td style="width: 50%; border: none;"> <input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan drug designation </td> <td style="width: 50%; border: none;"> <input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Direct-to-OTC </td> </tr> </table> <p>NDAs: Subpart H <input type="checkbox"/> Accelerated approval (21 CFR 314.510) <input type="checkbox"/> Restricted distribution (21 CFR 314.520) Subpart I <input type="checkbox"/> Approval based on animal studies</p> <p><input type="checkbox"/> Submitted in response to a PMR <input type="checkbox"/> Submitted in response to a PMC <input type="checkbox"/> Submitted in response to a Pediatric Written Request</p> <p>Comments:</p>		<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan drug designation	<input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Direct-to-OTC
<input type="checkbox"/> Fast Track <input type="checkbox"/> Rolling Review <input checked="" type="checkbox"/> Orphan drug designation	<input type="checkbox"/> Rx-to-OTC full switch <input type="checkbox"/> Rx-to-OTC partial switch <input type="checkbox"/> Direct-to-OTC		
❖ BLAs only: Ensure <i>RMS-BLA Product Information Sheet for TBP</i> and <i>RMS-BLA Facility Information Sheet for TBP</i> have been completed and forwarded to OPI/OBI/DRM (Vicky Carter)	<input type="checkbox"/> Yes, dates		
❖ BLAs only: Is the product subject to official FDA lot release per 21 CFR 610.2 (<i>approvals only</i>)	<input type="checkbox"/> Yes <input type="checkbox"/> No		
Public communications (<i>approvals only</i>)			
<ul style="list-style-type: none"> • Office of Executive Programs (OEP) liaison has been notified of action 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		
<ul style="list-style-type: none"> • Press Office notified of action (by OEP) 	<input checked="" type="checkbox"/> Yes <input type="checkbox"/> No		
<ul style="list-style-type: none"> • Indicate what types (if any) of information dissemination are anticipated 	<input type="checkbox"/> None <input checked="" type="checkbox"/> HHS Press Release <input type="checkbox"/> FDA Talk Paper <input checked="" type="checkbox"/> CDER Q&As <input type="checkbox"/> Other		

² Answer all questions in all sections in relation to the pending application, i.e., if the pending application is an NDA or BLA supplement, then the questions should be answered in relation to that supplement, not in relation to the original NDA or BLA. For example, if the application is a pending BLA supplement, then a new *RMS-BLA Product Information Sheet for TBP* must be completed.

❖ Exclusivity	
<ul style="list-style-type: none"> Is approval of this application blocked by any type of exclusivity? 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes
<ul style="list-style-type: none"> NDA and BLAs: Is there existing orphan drug exclusivity for the “same” drug or biologic for the proposed indication(s)? <i>Refer to 21 CFR 316.3(b)(13) for the definition of “same drug” for an orphan drug (i.e., active moiety). This definition is NOT the same as that used for NDA chemical classification.</i> 	<input checked="" type="checkbox"/> No <input type="checkbox"/> Yes If, yes, NDA/BLA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 5-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 3-year exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> (b)(2) NDAs only: Is there remaining 6-month pediatric exclusivity that would bar effective approval of a 505(b)(2) application? <i>(Note that, even if exclusivity remains, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date exclusivity expires:
<ul style="list-style-type: none"> NDAs only: Is this a single enantiomer that falls under the 10-year approval limitation of 505(u)? <i>(Note that, even if the 10-year approval limitation period has not expired, the application may be tentatively approved if it is otherwise ready for approval.)</i> 	<input type="checkbox"/> No <input type="checkbox"/> Yes If yes, NDA # and date 10- year limitation expires:
❖ Patent Information (NDAs only)	
<ul style="list-style-type: none"> Patent Information: Verify that form FDA-3542a was submitted for patents that claim the drug for which approval is sought. If the drug is an old antibiotic, skip the Patent Certification questions. 	<input checked="" type="checkbox"/> Verified <input type="checkbox"/> Not applicable because drug is an old antibiotic.
<ul style="list-style-type: none"> Patent Certification [505(b)(2) applications]: Verify that a certification was submitted for each patent for the listed drug(s) in the Orange Book and identify the type of certification submitted for each patent. 	21 CFR 314.50(i)(1)(i)(A) <input type="checkbox"/> Verified 21 CFR 314.50(i)(1) <input type="checkbox"/> (ii) <input type="checkbox"/> (iii)
<ul style="list-style-type: none"> [505(b)(2) applications] If the application includes a paragraph III certification, it cannot be approved until the date that the patent to which the certification pertains expires (but may be tentatively approved if it is otherwise ready for approval). 	<input type="checkbox"/> No paragraph III certification Date patent will expire
<ul style="list-style-type: none"> [505(b)(2) applications] For each paragraph IV certification, verify that the applicant notified the NDA holder and patent owner(s) of its certification that the patent(s) is invalid, unenforceable, or will not be infringed (review documentation of notification by applicant and documentation of receipt of notice by patent owner and NDA holder). <i>(If the application does not include any paragraph IV certifications, mark “N/A” and skip to the next section below (Summary Reviews)).</i> 	<input type="checkbox"/> N/A (no paragraph IV certification) <input type="checkbox"/> Verified

- [505(b)(2) applications] For **each paragraph IV** certification, based on the questions below, determine whether a 30-month stay of approval is in effect due to patent infringement litigation.

Answer the following questions for **each** paragraph IV certification:

- (1) Have 45 days passed since the patent owner’s receipt of the applicant’s notice of certification?

Yes No

(Note: The date that the patent owner received the applicant’s notice of certification can be determined by checking the application. The applicant is required to amend its 505(b)(2) application to include documentation of this date (e.g., copy of return receipt or letter from recipient acknowledging its receipt of the notice) (see 21 CFR 314.52(e)).

If “Yes,” skip to question (4) below. If “No,” continue with question (2).

- (2) Has the patent owner (or NDA holder, if it is an exclusive patent licensee) submitted a written waiver of its right to file a legal action for patent infringement after receiving the applicant’s notice of certification, as provided for by 21 CFR 314.107(f)(3)?

Yes No

If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip the rest of the patent questions.

If “No,” continue with question (3).

- (3) Has the patent owner, its representative, or the exclusive patent licensee filed a lawsuit for patent infringement against the applicant?

Yes No

(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)).

If “No,” the patent owner (or NDA holder, if it is an exclusive patent licensee) has until the expiration of the 45-day period described in question (1) to waive its right to bring a patent infringement action or to bring such an action. After the 45-day period expires, continue with question (4) below.

- (4) Did the patent owner (or NDA holder, if it is an exclusive patent licensee) submit a written waiver of its right to file a legal action for patent infringement within the 45-day period described in question (1), as provided for by 21 CFR 314.107(f)(3)?

Yes No

If “Yes,” there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).

If “No,” continue with question (5).

<p>(5) Did the patent owner, its representative, or the exclusive patent licensee bring suit against the (b)(2) applicant for patent infringement within 45 days of the patent owner's receipt of the applicant's notice of certification?</p> <p>(Note: This can be determined by confirming whether the Division has received a written notice from the (b)(2) applicant (or the patent owner or its representative) stating that a legal action was filed within 45 days of receipt of its notice of certification. The applicant is required to notify the Division in writing whenever an action has been filed within this 45-day period (see 21 CFR 314.107(f)(2)). If no written notice appears in the NDA file, confirm with the applicant whether a lawsuit was commenced within the 45-day period).</p> <p><i>If "No," there is no stay of approval based on this certification. Analyze the next paragraph IV certification in the application, if any. If there are no other paragraph IV certifications, skip to the next section below (Summary Reviews).</i></p> <p><i>If "Yes," a stay of approval may be in effect. To determine if a 30-month stay is in effect, consult with the OND ADRA and attach a summary of the response.</i></p>	<p><input type="checkbox"/> Yes <input type="checkbox"/> No</p>
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CONTENTS OF ACTION PACKAGE

❖ Copy of this Action Package Checklist ³	10/27/2011
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Officer/Employee List

❖ List of officers/employees who participated in the decision to approve this application and consented to be identified on this list (<i>approvals only</i>)	<input checked="" type="checkbox"/> Included
Documentation of consent/non-consent by officers/employees	<input checked="" type="checkbox"/> Included

Action Letters

❖ Copies of all action letters (<i>including approval letter with final labeling</i>)	Approval letter 10/21/2011
---	----------------------------

Labeling

❖ Package Insert (<i>write submission/communication date at upper right of first page of PI</i>)	
<ul style="list-style-type: none"> • Most recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	10/20/2011
<ul style="list-style-type: none"> • Original applicant-proposed labeling 	12/23/2010
<ul style="list-style-type: none"> • Example of class labeling, if applicable 	none

³ Fill in blanks with dates of reviews, letters, etc.

Medication Guide/Patient Package Insert/Instructions for Use/Device Labeling (<i>write submission/communication date at upper right of first page of each piece</i>)	<input checked="" type="checkbox"/> Medication Guide <input checked="" type="checkbox"/> Patient Package Insert <input type="checkbox"/> Instructions for Use <input type="checkbox"/> Device Labeling <input type="checkbox"/> None
<ul style="list-style-type: none"> Most-recent draft labeling. If it is division-proposed labeling, it should be in track-changes format. 	Same document as package insert
<ul style="list-style-type: none"> Original applicant-proposed labeling 	Same document as package insert
<ul style="list-style-type: none"> Example of class labeling, if applicable 	none
❖ Labels (full color carton and immediate-container labels) (<i>write submission/communication date on upper right of first page of each submission</i>)	
<ul style="list-style-type: none"> Most-recent draft labeling 	10/17/2011
❖ Proprietary Name <ul style="list-style-type: none"> Acceptability/non-acceptability letter(s) (<i>indicate date(s)</i>) Review(s) (<i>indicate date(s)</i>) Ensure that both the proprietary name(s), if any, and the generic name(s) are listed in the Application Product Names section of DARRTS, and that the proprietary/trade name is checked as the 'preferred' name. 	09/23/2011; 06/06/2011; 05/26/2011
❖ Labeling reviews (<i>indicate dates of reviews and meetings</i>)	<input checked="" type="checkbox"/> RPM 08/11/2011 <input checked="" type="checkbox"/> DMEPA 8/29/2011; 05/26/2011 <input checked="" type="checkbox"/> DRISK 10/5/2011 <input checked="" type="checkbox"/> DDMAC 10/6/2011 (MG); 09/28/2011(PI) <input checked="" type="checkbox"/> SEALD 10/23/2011; 10/20/2011 <input checked="" type="checkbox"/> CSS (see CSS review memo - 09/16/2011—section G) <input type="checkbox"/> Other reviews
Administrative / Regulatory Documents	
❖ Administrative Reviews (<i>e.g., RPM Filing Review⁴/Memo of Filing Meeting</i>) (<i>indicate date of each review</i>)	10/20/2011(RPM filing review) 01/26/2011 non-clinical filing review
❖ All NDA (b)(2) Actions: Date each action cleared by (b)(2) Clearance Cmte	
❖ NDA (b)(2) Approvals Only: 505(b)(2) Assessment (<i>indicate date</i>)	<input checked="" type="checkbox"/> Not a (b)(2) <input checked="" type="checkbox"/> Not a (b)(2)
❖ NDAs only: Exclusivity Summary (<i>signed by Division Director</i>)	<input checked="" type="checkbox"/> Included
❖ Application Integrity Policy (AIP) Status and Related Documents http://www.fda.gov/ICECI/EnforcementActions/ApplicationIntegrityPolicy/default.htm	
<ul style="list-style-type: none"> Applicant is on the AIP 	<input type="checkbox"/> Yes <input checked="" type="checkbox"/> No
<ul style="list-style-type: none"> This application is on the AIP <ul style="list-style-type: none"> If yes, Center Director's Exception for Review memo (<i>indicate date</i>) If yes, OC clearance for approval (<i>indicate date of clearance communication</i>) 	<input type="checkbox"/> Yes <input type="checkbox"/> No <input type="checkbox"/> Not an AP action

⁴ Filing reviews for scientific disciplines should be filed behind the respective discipline tab.

❖ Pediatrics (<i>approvals only</i>) <ul style="list-style-type: none"> Date reviewed by PeRC <u>N/A</u> If PeRC review not necessary, explain: <u>Orphan indication--waived</u> Pediatric Page/Record (<i>approvals only, must be reviewed by PERC before finalized</i>) 	<input checked="" type="checkbox"/> Included 10/06/11 (OK by PERC (GG) on 10/6/2011)
❖ Debarment certification (original applications only): verified that qualifying language was not used in certification and that certifications from foreign applicants are cosigned by U.S. agent (<i>include certification</i>)	<input checked="" type="checkbox"/> Verified, statement is acceptable
❖ Outgoing communications (<i>letters (except action letters), emails, faxes, telecons</i>)	Multiple emails
❖ Internal memoranda, telecons, etc.	none
❖ Minutes of Meetings	
• Regulatory Briefing (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> No mtg
• If not the first review cycle, any end-of-review meeting (<i>indicate date of mtg</i>)	<input checked="" type="checkbox"/> N/A
• Pre-NDA/BLA meeting (<i>indicate date of mtg</i>)	08/30/2010
• EOP2 meeting (<i>indicate date of mtg</i>)	05/09/2007
• Other milestone meetings (e.g., EOP2a, CMC pilots) (<i>indicate dates of mtgs</i>)	Pre-IND meeting 10/13/2004
❖ Advisory Committee Meeting(s)	<input checked="" type="checkbox"/> No AC meeting
• Date(s) of Meeting(s)	
• 48-hour alert or minutes, if available (<i>do not include transcript</i>)	
Decisional and Summary Memos	
Office Director Decisional Memo (<i>indicate date for each review</i>)	10/21/2011
Division Director Summary Review (<i>indicate date for each review</i>)	09/25/2011
Cross-Discipline Team Leader Review (<i>indicate date for each review</i>)	10/19/2011
PMR/PMC Development Templates (<i>indicate total number</i>)	10/20/2011
Clinical Information⁵	
❖ Clinical Reviews	
• Clinical Team Leader Review(s) (<i>indicate date for each review</i>)	Clinical (see CDTL review) Safety (08/31/11)
• Clinical review(s) (<i>indicate date for each review</i>)	10/04/11 (clinical); 08/24/11 (safety review)
• Social scientist review(s) (if OTC drug) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Financial Disclosure reviews(s) or location/date if addressed in another review OR If no financial disclosure information was required, check here <input type="checkbox"/> and include a review/memo explaining why not (<i>indicate date of review/memo</i>)	See clinical review (10/14/11)
❖ Clinical reviews from immunology and other clinical areas/divisions/Centers (<i>indicate date of each review</i>)	QT review 09/09/11; Pharmacovigilant review 8/3/11
❖ Controlled Substance Staff review(s) and Scheduling Recommendation (<i>indicate date of each review</i>)	09/16/2011

⁵ Filing reviews should be filed with the discipline reviews.

❖ Risk Management <ul style="list-style-type: none"> REMS Documents and Supporting Statement (<i>indicate date(s) of submission(s)</i>) REMS Memo(s) and letter(s) (<i>indicate date(s)</i>) Risk management review(s) and recommendations (including those by OSE and CSS) (<i>indicate date of each review and indicate location/date if incorporated into another review</i>) 	<input checked="" type="checkbox"/> None
❖ DSI Clinical Inspection Review Summary(ies) (<i>include copies of DSI letters to investigators</i>)	10/5/2011; 07/27/11; 07/26/11; 07/20/11; 07/07/11
Clinical Microbiology <input checked="" type="checkbox"/> None	
❖ Clinical Microbiology Team Leader Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Clinical Microbiology Review(s) (<i>indicate date for each review</i>)	<input type="checkbox"/> None
Biostatistics <input type="checkbox"/> None	
❖ Statistical Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Statistical Review(s) (<i>indicate date for each review</i>)	09/06/11
Clinical Pharmacology <input type="checkbox"/> None	
❖ Clinical Pharmacology Division Director Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology Team Leader Review(s) (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
Clinical Pharmacology review(s) (<i>indicate date for each review</i>)	10/23/11; 10/9/11
❖ DSI Clinical Pharmacology Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None
Nonclinical <input type="checkbox"/> None	
❖ Pharmacology/Toxicology Discipline Reviews	
• ADP/T Review(s) (<i>indicate date for each review</i>)	10/20/11
• Supervisory Review(s) (<i>indicate date for each review</i>)	10/17/11
• Pharm/tox review(s), including referenced IND reviews (<i>indicate date for each review</i>)	10/14/11
❖ Review(s) by other disciplines/divisions/Centers requested by P/T reviewer (<i>indicate date for each review</i>)	<input checked="" type="checkbox"/> None
❖ Statistical review(s) of carcinogenicity studies (<i>indicate date for each review</i>)	10/14/11
❖ ECAC/CAC report/memo of meeting	9/28/11
❖ DSI Nonclinical Inspection Review Summary (<i>include copies of DSI letters</i>)	<input checked="" type="checkbox"/> None requested

Product Quality		<input type="checkbox"/> None
❖ Product Quality Discipline Reviews		
• ONDQA/OBP Division Director Review(s) <i>(indicate date for each review)</i>		10/21/11
• Branch Chief/Team Leader Review(s) <i>(indicate date for each review)</i>		<input checked="" type="checkbox"/> None
• Product quality review(s) including ONDQA biopharmaceutics reviews <i>(indicate date for each review)</i>		08/04/11; 08/02/11
❖ Microbiology Reviews <input type="checkbox"/> NDAs: Microbiology reviews (sterility & pyrogenicity) (OPS/NDMS) <i>(indicate date of each review)</i> <input type="checkbox"/> BLAs: Sterility assurance, microbiology, facilities reviews (DMPQ/MAPCB/BMT) <i>(indicate date of each review)</i>		<input checked="" type="checkbox"/> Not needed
❖ Reviews by other disciplines/divisions/Centers requested by CMC/quality reviewer <i>(indicate date of each review)</i>		<input checked="" type="checkbox"/> None
❖ Environmental Assessment (check one) (original and supplemental applications)		
<input checked="" type="checkbox"/> Categorical Exclusion <i>(indicate review date)(all original applications and all efficacy supplements that could increase the patient population)</i>		See CMC review
<input type="checkbox"/> Review & FONSI <i>(indicate date of review)</i>		N/A
<input type="checkbox"/> Review & Environmental Impact Statement <i>(indicate date of each review)</i>		N/A
❖ Facilities Review/Inspection		
<input checked="" type="checkbox"/> NDAs: Facilities inspections (include EER printout) <i>(date completed must be within 2 years of action date) (only original NDAs and supplements that include a new facility or a change that affects the manufacturing sites⁶)</i>		Date completed: 10/18/11 <input checked="" type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation <input type="checkbox"/> Not applicable
<input type="checkbox"/> BLAs: TB-EER <i>(date of most recent TB-EER must be within 30 days of action date) (original and supplemental BLAs)</i>		Date completed: <input type="checkbox"/> Acceptable <input type="checkbox"/> Withhold recommendation
❖ NDAs: Methods Validation <i>(check box only, do not include documents)</i>		<input checked="" type="checkbox"/> Completed <input type="checkbox"/> Requested <input type="checkbox"/> Not yet requested <input type="checkbox"/> Not needed (per review)

⁶ I.e., a new facility or a change in the facility, or a change in the manufacturing process in a way that impacts the Quality Management Systems of the facility.

Appendix to Action Package Checklist

An NDA or NDA supplemental application is likely to be a 505(b)(2) application if:

- (1) It relies on published literature to meet any of the approval requirements, and the applicant does not have a written right of reference to the underlying data. If published literature is cited in the NDA but is not necessary for approval, the inclusion of such literature will not, in itself, make the application a 505(b)(2) application.
- (2) **Or** it relies for approval on the Agency's previous findings of safety and efficacy for a listed drug product and the applicant does not own or have right to reference the data supporting that approval.
- (3) **Or** it relies on what is "generally known" or "scientifically accepted" about a class of products to support the safety or effectiveness of the particular drug for which the applicant is seeking approval. (Note, however, that this does not mean *any* reference to general information or knowledge (e.g., about disease etiology, support for particular endpoints, methods of analysis) causes the application to be a 505(b)(2) application.)

Types of products for which 505(b)(2) applications are likely to be submitted include: fixed-dose combination drug products (e.g., heart drug and diuretic (hydrochlorothiazide) combinations); OTC monograph deviations (see 21 CFR 330.11); new dosage forms; new indications; and, new salts.

An efficacy supplement can be either a (b)(1) or a (b)(2) regardless of whether the original NDA was a (b)(1) or a (b)(2).

An efficacy supplement is a 505(b)(1) supplement if the supplement contains all of the information needed to support the approval of the change proposed in the supplement. For example, if the supplemental application is for a new indication, the supplement is a 505(b)(1) if:

- (1) The applicant has conducted its own studies to support the new indication (or otherwise owns or has right of reference to the data/studies).
- (2) **And** no additional information beyond what is included in the supplement or was embodied in the finding of safety and effectiveness for the original application or previously approved supplements is needed to support the change. For example, this would likely be the case with respect to safety considerations if the dose(s) was/were the same as (or lower than) the original application.
- (3) **And** all other "criteria" are met (e.g., the applicant owns or has right of reference to the data relied upon for approval of the supplement, the application does not rely for approval on published literature based on data to which the applicant does not have a right of reference).

An efficacy supplement is a 505(b)(2) supplement if:

- (1) Approval of the change proposed in the supplemental application would require data beyond that needed to support our previous finding of safety and efficacy in the approval of the original application (or earlier supplement), and the applicant has not conducted all of its own studies for approval of the change, or obtained a right to reference studies it does not own. For example, if the change were for a new indication AND a higher dose, we would likely require clinical efficacy data and preclinical safety data to approve the higher dose. If the applicant provided the effectiveness data, but had to rely on a different listed drug, or a new aspect of a previously cited listed drug, to support the safety of the new dose, the supplement would be a 505(b)(2).
- (2) **Or** the applicant relies for approval of the supplement on published literature that is based on data that the applicant does not own or have a right to reference. If published literature is cited in the supplement but is not necessary for approval, the inclusion of such literature will not, in itself, make the supplement a 505(b)(2) supplement.
- (3) **Or** the applicant is relying upon any data they do not own or to which they do not have right of reference.

If you have questions about whether an application is a 505(b)(1) or 505(b)(2) application, consult with your ODE's ADRA.

This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SU-LIN SUN
10/28/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, October 27, 2011 6:09 PM
To: 'Jeanine M. Swalec'
Subject: RE: NDA 202067 PMC

Dear Jenny:

Our review team confirmed that there is no need for Clin Pharm PMC/PMR for the in vitro study evaluating the CYP2C8 and CYP2B^A induction potential by CLB and N-desmethyloclobazam as a Phase 4 commitment at the time of this NDA approval.

thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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From: Jeanine M. Swalec [<mailto:JSWA@Lundbeck.com>]
Sent: Thursday, October 20, 2011 11:11 PM
To: Sun, Su-Lin
Subject: NDA 202067 PMC

Dear Sulin,

In the Pre-NDA minutes from our August 31, 2010, we agreed to conduct a P-gp substrate study as a PMC/PMR.

In a July 7, 2011 email from you, you notified us that it was acceptable to conduct an in vitro study evaluating the CYP2C8 and CYP2B⁶ induction potential by CLB and N-CLB as a Phase 4 commitment.

Should we still expect a request from you for proposed dates for these studies?

Thanks in advance! Jenny

Jeanine M. Swalec

Sr. Director, Global Regulatory Lead
US Development Strategy



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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

SU-LIN SUN
10/27/2011

Sun, Su-Lin

From: Jeanine M. Swalec [JSWA@Lundbeck.com]
Sent: Wednesday, October 26, 2011 11:37 AM
To: Sun, Su-Lin
Subject: RE: NDA 202067 ONFI

Dear Sulin,

Email received!

Thanks, Jenny

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Wednesday, October 26, 2011 9:40 AM
To: Jeanine M. Swalec
Subject: NDA 202067 ONFI
Importance: High

Dear Jenny:

Our Clin Pharm team would like me to send this document to you, please send me an email back to confirm receipt of this document (ONFI burst).

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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From the American College of Clinical Pharmacology

In cooperation with the Food and Drug Administration (FDA), and as a service to our members, ACCP will periodically distribute information about newly approved therapies or significant changes to approved therapies. This helps FDA to inform professionals in the patient care arena of recent approvals in a timely manner. Included in the email from the FDA will be a link to the product label, which will provide the relevant clinical pharmacology information on the indication, contraindications, dosing, and safety. In sending this information, ACCP does not endorse any product or therapy and does not take any position on the safety or efficacy of the product or therapy described.

FDA Approval of ONFI™ (clobazam) for Adjunctive Therapy for the Treatment of Seizures Associated with Lennox-Gastaut Syndrome (LGS)

On October 21, 2011, the FDA approved ONFI™ (clobazam) as an adjunctive therapy for the treatment of seizures associated with Lennox-Gastaut syndrome (LGS) in patients ≥ 2 years of age. Clobazam is an antiepileptic drug of the benzodiazepine class. It has been approved in other countries since the late 1970's for the treatment of anxiety and epilepsy, and received Orphan drug designation on December 18, 2007, for the treatment of LGS in the U.S.

The effectiveness and safety of ONFI for the adjunctive treatment for LGS was evaluated in two controlled studies in about 300 patients with LGS. The exposure-response analysis of these data indicated that there are clear exposure-response relationships for both efficacy and safety. All three studied dose groups (10 mg, 20 mg, and 40 mg per day) were statistically significantly superior to the placebo groups with regard to the drop seizure rates, the primary efficacy endpoint. This effect was in a dose-dependent manner, with the greatest mean seizure reduction observed at the highest studied dose of 40mg/day. Sedation-related adverse events (i.e., sedation, somnolence, sleepiness, drowsiness, lethargy and listlessness) were the most common adverse reactions. Results showed that patients assigned to doses greater than 5 mg/day experienced a higher percentage of sedation-related adverse events than the placebo group. However, no significant difference between 20 mg/day and 40mg/day doses was observed.

ONFI should be administered in divided doses twice daily (the 5 mg dose can be administered as a single daily dose) and should be dosed according to body weight. Within each body weight group, dosing should be individualized based on clinical efficacy and tolerability. Dose escalation should not proceed more rapidly than weekly, because serum concentrations of clobazam and its active metabolite require 5 and 9 days, respectively, to reach steady-state.

Table 1. Recommended Total Daily Dosing by Weight Group

	≤ 30 kg Body Weight	>30 kg Body Weight
Starting Dose	5 mg	10 mg

Starting Day 7	10 mg	20 mg
Starting Day 14	20 mg	40 mg

Clobazam is extensively metabolized in the liver, with 82% of the administered dose recovered in urine (2% unchanged) and 11% in feces (1% unchanged). The major metabolic pathway of clobazam involves N-demethylation, primarily by CYP3A4 and to a lesser extent by CYP2C19 and CYP2B6. N-desmethyloclobazam, known to have intrinsic benzodiazepine like activity, is the major circulating metabolite in humans, and its plasma concentrations are 3-5 times higher than those of clobazam. This metabolite is further metabolized by CYP2C19. In CYP2C19 poor metabolizers, levels of N-desmethyloclobazam were 3-5-fold higher than that in CYP2C19 extensive metabolizers. In healthy adults and patients, the mean terminal half-life of clobazam ($t_{1/2}$) is 36 to 42 hours. The mean terminal half-life of N-desmethyloclobazam is 71 to 82 hours.

Clobazam is an inhibitor of CYP2D6; thus, drugs metabolized by CYP2D6 may require dose adjustment when used with ONFI. Clobazam is a mild inducer of CYP3A4; dose adjustments are unnecessary for most CYP3A4 substrates considering the relatively small inducing effect. However, the effectiveness of some hormonal contraceptives metabolized by CYP3A4 may be diminished when given with ONFI. Additional non-hormonal forms of contraception are recommended when using ONFI.

Because the active metabolite N-desmethyloclobazam is primarily metabolized by CYP 2C19, dosage adjustment is recommended when strong and moderate CYP2C19 inhibitors are used concomitantly with ONFI.

CYP3A4 inducers (phenobarbital, phenytoin, and carbamazepine), CYP2C9 inducers (valproic acid, phenobarbital, phenytoin, and carbamazepine), and CYP2C9 inhibitors (felbamate and oxcarbazepine) had no significant impact on the pharmacokinetics of clobazam and N-desmethyloclobazam.

Dosing adjustments (i.e., starting dose at 5 mg/day, then be titrated according to weight, but to half the dose presented in Table 1 as tolerated; if necessary and based upon clinical response, an additional titration to the maximum dose [20 mg/day or 40 mg/day, depending on weight] may be started on day 21) are recommended for the following specific populations:

- Geriatric patients had slower clobazam clearance, thus dosing adjustment is recommended.
- CYP2C19 poor metabolizers had approximately 3- to 5-fold higher N-desmethyloclobazam exposure (C_{max} and AUC), compared to extensive metabolizers, respectively, with insignificant change in exposure to the parent drug. Dosing adjustment is recommended for patients who are known to be CYP2C19 poor metabolizers.
- Clobazam is primarily metabolized in the liver. Dosing in patients with hepatic impairment should be adjusted for mild and moderate hepatic impairment patients.

No dosing recommendation can be provided for patients with severe hepatic impairment because of inadequate data.

The exposure (C_{\max} and AUC) of clobazam and N-desmethyloclobazam were not significantly increased in patients with mild or moderate renal impairment in a dedicated study; therefore, no dosing adjustment is recommended for patients with mild and moderate renal impairment. There is no experience with ONFI in patients with severe renal impairment or end stage renal disease (ESRD). It is not known if clobazam or N-desmethyloclobazam is dialyzable.

Full prescribing information is available at:

http://www.accessdata.fda.gov/drugsatfda_docs/label/2011/202067s0001bl.pdf

*By Ta-Chen Wu, Senior Clinical Pharmacologist, Angela Yuxin Men, Team Leader,
Division of Clinical Pharmacology 1, Office of Clinical Pharmacology, Office of
Translational Sciences, CDER, FDA*

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/s/

SU-LIN SUN
10/26/2011

Sun, Su-Lin

From: Jeanine M. Swalec [JSWA@Lundbeck.com]
Sent: Friday, October 21, 2011 5:18 PM
To: Sun, Su-Lin
Subject: RE: NDA 202067

Dear Sulin,

I have received the NDA approval letter.

Thanks! Jenny

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Friday, October 21, 2011 4:10 PM
To: Jeanine M. Swalec
Subject: NDA 202067
Importance: High

Dear Jenny:

Attached is an electronic copy of the approval letter for NDA 202067 Onfi (clobazam) tablet. Please send me an email back to acknowledge that you have receive this notification. You will receive the official document via mail in few days.

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
10/21/2011

Sun, Su-Lin

From: Jeanine M. Swalec [JSWA@Lundbeck.com]
Sent: Friday, October 21, 2011 4:19 PM
To: Sun, Su-Lin
Subject: RE: NDA 202067 FDA proposed final PI/MG

Dear Sulin,

We agree with your final PI/MG.

Thanks! Jenny

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Friday, October 21, 2011 3:17 PM
To: Jeanine M. Swalec
Subject: RE: NDA 202067 FDA proposed final PI/MG

Please take one more look and let me know whether you agree with this version of PI/MG.

thanks,
Sulin

From: Jeanine M. Swalec [mailto:JSWA@Lundbeck.com]
Sent: Friday, October 21, 2011 4:03 PM
To: Sun, Su-Lin
Subject: RE: NDA 202067 FDA proposed final PI/MG

Dear Sulin,

Attached is our proposed final PI/MG. Note that there are 2 track changes.

(1) HIGHLIGHTS 5.1
(2) FPI Section 5.1 title

Please advise what I need to do next!

Thanks

Jenny

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Friday, October 21, 2011 2:01 PM
To: Jeanine M. Swalec
Subject: NDA 202067 FDA proposed final PI/MG
Importance: High

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

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/s/

SU-LIN SUN
10/21/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, October 21, 2011 9:58 AM
To: 'Jeanine M. Swalec'
Subject: NDA 202067 urgent FDA information request

Importance: High

Dear Jenny:

Per our review team,, please provide us with a label that identical to your last counter-proposal PI, but replacing the Figure 2 (b) (4) histogram with one that only includes drop attacks. We need this before our 1 PM meeting this afternoon.

In additional, please have your team standby for possible Tcon between 1:30 to 3:00pm. Please please me with a Tcon #.

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
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/s/

SU-LIN SUN
10/27/2011

Sun, Su-Lin

From: Jeanine M. Swalec [JSWA@Lundbeck.com]
Sent: Wednesday, October 19, 2011 2:47 PM
To: Sun, Su-Lin
Subject: Re: NDA 202067 urgent information request-additional parameter

Hi Sulin,

My biometrics team assures me that is what they are producing.

Jenny

From: Sun, Su-Lin <Su-Lin.Sun@fda.hhs.gov>
To: Jeanine M. Swalec
Sent: Wed Oct 19 14:37:52 2011
Subject: RE: NDA 202067 urgent information request-additional parameter

Dear Jenny:

I just receive another reminder from our review team, that the request dataset is for the "seizure count" to be all drop seizures, the ones that count in the primary endpoint.

thanks,
Sulin

From: Jeanine M. Swalec [mailto:JSWA@Lundbeck.com]
Sent: Wednesday, October 19, 2011 11:55 AM
To: Sun, Su-Lin
Subject: RE: NDA 202067 urgent information request-additional parameter

Dear Sulin,

Our Biometrics department is working on this now. We can email you the dataset in an excel file for your review team this afternoon and/or we can officially submit via the FDA gateway the dataset in an .xpt file. Uploading will take longer.

Please advise as to what you would prefer.

Thanks! Jenny

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Wednesday, October 19, 2011 9:35 AM
To: Jeanine M. Swalec
Subject: RE: NDA 202067 urgent information request-additional parameter
Importance: High

Dear Jenny:

Our review team would like me to remind you about our requested derived dataset, please see below

"seizures" in that dataset are total drop seizures - the ones used for the primary ep

thanks,
Sulin

From: Jeanine M. Swalec [mailto:JSWA@Lundbeck.com]
Sent: Tuesday, October 18, 2011 11:49 PM
To: Sun, Su-Lin
Subject: Re: NDA 202067 urgent information request

Dear Sulin,

I'll convey your request to my team and we will plan to submit this specific derived dataset tomorrow as early in the day as possible

Jenny

From: Sun, Su-Lin <Su-Lin.Sun@fda.hhs.gov>
To: Jeanine M. Swalec
Sent: Tue Oct 18 23:32:51 2011
Subject: NDA 202067 urgent information request

Dear Jenny,

Thank you for your rapid response on this! We would like to take you up on your offer for a derived data set. For each subject in study 1012, please provide seizure counts as follows, using this basic architecture:

Subject	period	seizure count	days	seizure rate
0001	baseline	xxxx	yyyy	zzzz
0001	week 5	hhhh	iiii	jjjj
0001	week 7
0001	week 9	etc		
0001	week 11	etc		
0001	week 13	etc		
0001	week 15 ET	etc		
0001	maintenance	ss	tt	uu
0002	baseline	xxxx	yyyy	zzzz
0002	week 5	hhhh	iiii	jjjj
0002	week 7
0002	week 9	etc		
0002	week 11	etc		
0002	week 13	etc		
0002	week 15 ET	etc		
0002	maintenance	ss	tt	uu

We would appreciate having all periods listed for all subjects. If there are no data for a subject during a given period, please include the period, with some notation to convey that there were no data (i.e., you could enter a dot ". ").

Thank you for your assistance with these late requests.

thanks,

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/s/

SU-LIN SUN
10/21/2011

From: [Sun, Su-Lin](#)
To: ["Jeanine M. Swalec";](#)
Subject: NDA 202067
Date: Wednesday, October 19, 2011 5:21:20 PM
Attachments: [NDA 202067 ONFI-FDA prposed PI sections 101911.doc](#)

Dear Jenny:

Attached document listed our proposed PI sections (5.3, 8.4, 9.1, 9.2, 9.3 and 11).

Once you send me your counter proposal of those sections, I will add to our PI prior our team meeting tomorrow.

If you have any question, please feel free to contact me.

Once again, thanks for all your help.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

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/s/

SU-LIN SUN
10/21/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Wednesday, October 19, 2011 10:35 AM
To: 'Jeanine M. Swalec'
Subject: RE: NDA 202067 urgent information request-additional parameter
Importance: High

Dear Jenny:

Our review team would like me to remind you about our requested derived dataset, please see below

"seizures" in that dataset are total drop seizures - the ones used for the primary ep

thanks,
 Sulin

From: Jeanine M. Swalec [mailto:JSWA@Lundbeck.com]
Sent: Tuesday, October 18, 2011 11:49 PM
To: Sun, Su-Lin
Subject: Re: NDA 202067 urgent information request

Dear Sulin,

I'll convey your request to my team and we will plan to submit this specific derived dataset tomorrow as early in the day as possible

Jenny

From: Sun, Su-Lin <Su-Lin.Sun@fda.hhs.gov>
To: Jeanine M. Swalec
Sent: Tue Oct 18 23:32:51 2011
Subject: NDA 202067 urgent information request

Dear Jenny,

Thank you for your rapid response on this! We would like to take you up on your offer for a derived data set. For each subject in study 1012, please provide seizure counts as follows, using this basic architecture:

Subject	period	seizure count	days	seizure rate
0001	baseline	xxxx	yyyy	zzzz
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0001	week 7
0001	week 9	etc		
0001	week 11	etc		
0001	week 13	etc		
0001	week 15 ET	etc		
0001	maintenance	ss	tt	uu
0002	baseline	xxxx	yyyy	zzzz
0002	week 5	hhhh	iiii	jjj

0002	week 7
0002	week 9	etc		
0002	week 11	etc		
0002	week 13	etc		
0002	week 15 ET	etc		
0002	maintenance	ss	tt	uu

We would appreciate having all periods listed for all subjects. If there are no data for a subject during a given period, please include the period, with some notation to convey that there were no data (i.e., you could enter a dot ". ").

Thank you for your assistance with these late requests.

thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
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Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

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/s/

SU-LIN SUN
10/21/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, October 18, 2011 12:13 PM
To: 'Jeanine M. Swalec'
Subject: NDA 202067 FDA's urgent information request

Importance: High

Attachments: Microsoft Office Word Document; Seizures from PDF_Final.xls

Dear Jenny:

Below are the urgent request from our review team for NDA 202067 Onfi (clobazam):

The review team has been trying to perform some exploratory efficacy analyses in study 1012, and we have been seizure rates during baseline and maintenance periods, found in NDA202067\0000\m5\datasets\ov-1012\analys

We could find two sources of the raw daily seizure data in your original submission:

- \0000\m5\datasets\ov-1012\tabulations\sdtm\FA.xpt
- \0000\m5\53-clin-stud-rep\535-rep-effic-safety-stud\lgs\5351-stud-rep-contr\ov-1012\ov-1012-16-2-6-ind-eff-r

We found information on dates/time in \0000\m5\datasets\ov-1012\tabulations\sdtm\SV.xpt.

When we analyzed data in FA.xpt and SV.xpt to derive seizure rates according to the Statistical Analysis Plan, we reproduce your mean seizure rates for the baseline and maintenance periods. We tried again using an independent the listings in ov-1012-16-2-6-ind-eff-resp-data.pdf directly, we could not reproduce your numbers. Moreover, there are inconsistencies between the pdf listings and FA.xpt.

An example of an inconsistency:

Subject 0003-7021

For subject 0003-7021, your seizure count for the maintenance period appears to be 45 in 62 days, for a seizure. From the data in FS.xpt, we count only 44 seizures. When we checked ov-1012-16-2-6-ind-eff-resp-data.pdf, we also an entry of "unknown" on 14JUL2008. For a single drop attack, "unknown" should be counted as 1, according to the Statistical Analysis Plan. Thus, accounting for the entry of "unknown" on 14JUL, the total would be 45, i.e., the number would be correct. However, there isn't an entry in FS.xpt that corresponds with the entry of "unknown" on 14JUL2008. Presumably, you have correct numbers, but we do not seem to have such a dataset.

For many subjects, we could not reproduce your means using FA.xpt.

We then used a second method: we took all of the listings in ov-1012-16-2-6-ind-eff-resp-data.pdf and created a seizure counts. Using this unsophisticated analysis, we were unable to reproduce your numbers.

The spreadsheet is attached. On the "summary" worksheet, the orange columns represent the results of the calculations for the baseline seizure rates, the green columns represent the results of calculations for the maintenance seizure rates. The white columns are the results of calculations for the baseline seizure rates using the data in ov_1012.xpt (using a VLOOKUP function). The 2 rightmost columns represent the differences between your calculations and our calculations.

Typically when we find discrepancies like this, we find out that we overlooked something and/or made a simple error.

Please review the spreadsheet, and help us understand why we are unable to generate your mean seizure rates using the data in ov-1012-16-2-6-ind-eff-resp-data.pdf or the data in FA.xpt.

We would like to understand this as soon as possible. After you have had a chance to review this, we would be happy to discuss this in a teleconference.



Seizures from
PDF_Final.xls (3...

If you have any question, please feel free to contact me.

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
10/21/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, October 18, 2011 10:55 AM
To: 'Jeanine M. Swalec'
Cc: Kelley, Laurie
Subject: NDA 202067 carton and container labels

Importance: High

Dear Jenny:

Per our review team, that your October 17, 2011 submission for carton and container label for NDA 202067 Onfi (clobazam) --has been found acceptable.

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
10/21/2011

NDA 202067 Nonclinical Post Marketing Requirements	Action	Lundbeck Proposed Dates
Embryo-fetal Development Study in Rat	Protocol Submission	September 2012
	Study Completion	April 2013
	Final Report Submission	August 2013
Prenatal and Postnatal Development (including maternal function) Study in Rat	Protocol Submission	September 2012
	Study Completion	March 2013
	Final Report Submission	August 2013
Fertility and Early Embryonic Development to Implantation Study in Rat	Protocol Submission	November 2012
	Study Completion	May 2013
	Final Report Submission	October 2013
Embryo-fetal Development Study in Rabbit	Protocol Submission	November 2012
	Study Completion	April 2013
	Final Report Submission	August 2013
Carcinogenicity Study in Rat	Protocol Submission	May 2013
	Study Completion	March 2015
	Final Report Submission	July 2016
Carcinogenicity Study in Mouse	Protocol Submission	August 2013
	Study Completion	June 2016
	Final Report Submission	October 2016

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/s/

SU-LIN SUN
10/21/2011

Sun, Su-Lin

From: Jeanine M. Swalec [JSWA@Lundbeck.com]
Sent: Monday, October 17, 2011 8:00 PM
To: Sun, Su-Lin
Subject: RE: NDA 202067 Nonclinical PMR
Attachments: 17OCT2011 Nonclinical PMRs_LB Proposed Dates.doc

Dear Sulin,

Please find attached a table listing the FDA's nonclinical PMRs with Lundbeck's proposed dates for final protocol submission, study completion, and final report submission.

Respectfully, Jenny

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Friday, October 14, 2011 4:29 PM
To: Jeanine M. Swalec
Subject: NDA 202067 PMR
Importance: High

Dear Jenny:

The following are the PMRs conveyed to you in this afternoon's telecon:

1. Fertility and early embryonic development to implantation study in rat.
2. Embryo-fetal development study in rat.
3. Embryo-fetal development study in rabbit.
4. Prenatal and postnatal development (including maternal function) study in rat.
5. Carcinogenicity study in mouse.
6. Carcinogenicity study in rat.

For each, the following dates will need to be provided:

Final protocol submission date:
Study completion date:
Final report date:

Please send me an email to acknowledge your agreement with the above PMRs for NDA 202067 ONFI (clobazam) tablet. Per our discussion during today's Tcon, you will send us the above dates by next week (Monday or Tuesday).

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
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Silver Spring, MD 20903

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NDA 202067 Nonclinical Post Marketing Requirements	Action	Lundbeck Proposed Dates
Embryo-fetal Development Study in Rat	Protocol Submission	September 2012
	Study Completion	April 2013
	Final Report Submission	August 2013
Prenatal and Postnatal Development (including maternal function) Study in Rat	Protocol Submission	September 2012
	Study Completion	March 2013
	Final Report Submission	August 2013
Fertility and Early Embryonic Development to Implantation Study in Rat	Protocol Submission	November 2012
	Study Completion	May 2013
	Final Report Submission	October 2013
Embryo-fetal Development Study in Rabbit	Protocol Submission	November 2012
	Study Completion	April 2013
	Final Report Submission	August 2013
Carcinogenicity Study in Rat	Protocol Submission	May 2013
	Study Completion	March 2015
	Final Report Submission	July 2016
Carcinogenicity Study in Mouse	Protocol Submission	August 2013
	Study Completion	June 2016
	Final Report Submission	October 2016

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/s/

SU-LIN SUN
10/21/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Monday, October 17, 2011 2:25 PM
To: 'Jeanine M. Swalec'
Subject: NDA 202067

Importance: High

Dear Jenny:

For section 12.3--

(b) (4)

(b) (4)

Renal Impairment

The effect of renal impairment on the pharmacokinetics of clobazam was evaluated in patients with mild (creatinine clearance [CL_{CR}] > 50 to 80 mL/min; N=6) and moderate (CL_{CR} = 30 to 50 mL/min; N=6) renal dysfunction, with matching healthy controls (N=6), following administration of multiple doses of ONFI 20 mg/day. There were insignificant changes in C_{max} (3-24%) and AUC ($\leq 13\%$) for clobazam or N-desmethyloclobazam in patients with mild or moderate renal impairment compared to patients with normal renal function. Patients with severe renal impairment or ESRD were not included in this study.

Thanks,

Sulin

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/s/

SU-LIN SUN
10/21/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, October 20, 2011 5:30 PM
To: 'Jeanine M. Swalec'
Subject: NDA 202067

Importance: High

Attachments: NDA 202067 Onfi--FDA proposed Labeling text dated 102011.doc

Dear Jenny:

Attached is our proposed PI/MG for NDA 202067 Onfi (clobazam).


NDA 202067
nfi--FDA proposed .

thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
10/20/2011

Sun, Su-Lin

From: Jeanine M. Swalec [JSWA@Lundbeck.com]
Sent: Wednesday, October 19, 2011 2:47 PM
To: Sun, Su-Lin
Subject: Re: NDA 202067 urgent information request-additional parameter

Hi Sulin,

My biometrics team assures me that is what they are producing.

Jenny

From: Sun, Su-Lin <Su-Lin.Sun@fda.hhs.gov>
To: Jeanine M. Swalec
Sent: Wed Oct 19 14:37:52 2011
Subject: RE: NDA 202067 urgent information request-additional parameter

Dear Jenny:

I just receive another reminder from our review team, that the request dataset is for the "seizure count" to be all drop seizures, the ones that count in the primary endpoint.

thanks,
Sulin

From: Jeanine M. Swalec [mailto:JSWA@Lundbeck.com]
Sent: Wednesday, October 19, 2011 11:55 AM
To: Sun, Su-Lin
Subject: RE: NDA 202067 urgent information request-additional parameter

Dear Sulin,

Our Biometrics department is working on this now. We can email you the dataset in an excel file for your review team this afternoon and/or we can officially submit via the FDA gateway the dataset in an .xpt file. Uploading will take longer.

Please advise as to what you would prefer.

Thanks! Jenny

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Wednesday, October 19, 2011 9:35 AM
To: Jeanine M. Swalec
Subject: RE: NDA 202067 urgent information request-additional parameter
Importance: High

Dear Jenny:

Sun, Su-Lin

From: Jeanine M. Swalec [JSWA@Lundbeck.com]
Sent: Tuesday, October 18, 2011 12:32 PM
To: Sun, Su-Lin
Subject: RE: NDA 202067 Nonclinical PMR

Dear Sulin,

My apologies, the study completion date should be March 2016.

Respectfully, Jenny

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Tuesday, October 18, 2011 11:20 AM
To: Jeanine M. Swalec
Subject: RE: NDA 202067 Nonclinical PMR
Importance: High

Dear Jenny:

Carcinogenicity Study in Rat	Protocol Submission	May 2013
	Study Completion	March 2015
	Final Report Submission	July 2016

Our review team would like me to check with you regard to your proposed study completion for carcinogenicity study in rat. Should the date be March 2016 instead of March 2015.

Please send me an email to confirm which date it should be.

thanks,

Su-Lin Sun, PharmD
 LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20993

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From: Jeanine M. Swalec [mailto:JSWA@Lundbeck.com]
Sent: Monday, October 17, 2011 8:00 PM
To: Sun, Su-Lin
Subject: RE: NDA 202067 Nonclinical PMR

Dear Sulin,

Please find attached a table listing the FDA's nonclinical PMRs with Lundbeck's proposed dates for final protocol submission, study completion, and final report submission.

Respectfully, Jenny

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Friday, October 14, 2011 4:29 PM
To: Jeanine M. Swalec
Subject: NDA 202067 PMR
Importance: High

Dear Jenny:

The following are the PMRs conveyed to you in this afternoon's telecon:

1. Fertility and early embryonic development to implantation study in rat.
2. Embryo-fetal development study in rat.
3. Embryo-fetal development study in rabbit.
4. Prenatal and postnatal development (including maternal function) study in rat.
5. Carcinogenicity study in mouse.
6. Carcinogenicity study in rat.

For each, the following dates will need to be provided:

Final protocol submission date:

Study completion date:

Final report date:

Please send me an email to acknowledge your agreement with the above PMRs for NDA 202067 ONFI (clobazam) tablet. Per our discussion during today's Tcon, you will send us the above dates by next week (Monday or Tuesday).

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
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APPEARS THIS WAY ON ORIGINAL

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/s/

SU-LIN SUN
10/20/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, October 14, 2011 5:29 PM
To: 'Jeanine M. Swalec'
Subject: NDA 202067

Importance: High

Dear Jenny:

The following are the PMRs conveyed to you in this afternoon's telecon:

1. Fertility and early embryonic development to implantation study in rat.
2. Embryo-fetal development study in rat.
3. Embryo-fetal development study in rabbit.
4. Prenatal and postnatal development (including maternal function) study in rat.
5. Carcinogenicity study in mouse.
6. Carcinogenicity study in rat.

For each, the following dates will need to be provided:

Final protocol submission date:

Study completion date:

Final report date:

Please send me an email to acknowledge your agreement with the above PMRs for NDA 202067 ONFI (clobazam) tablet. Per our discussion during today's Tcon, you will send us the above dates by next week (Monday or Tuesday).

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

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/s/

SU-LIN SUN
10/14/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, October 14, 2011 7:56 PM
To: Jeanine M. Swalec
Subject: NDA 202067

Importance: High

Attachments: NDA 202067 Onfi--FDA proposed labeling text 10142011.doc; NDA 202067 ONFI --FDA proposed MG 101411.doc

Dear Jenny:

Attached documents are our proposed PI and MG for NDA 202067 (Onfi).

(b) (4)

Once again, many thanks for your support and patience.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
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/s/

SU-LIN SUN
10/14/2011

Sun, Su-Lin

From: Jeanine M. Swalec [JSWA@Lundbeck.com]
Sent: Friday, October 14, 2011 6:49 PM
To: Sun, Su-Lin
Cc: Kelley, Laurie
Subject: RE: NDA 202067 carton and container label.

Dear Sulin, and Laurie,

We will make your requested change of [REDACTED] (b) (4); so please disregard my below request for clarification. We plan to submit on Monday a formal response to your request that will contain revised carton & container labels.

Have a good weekend!

Jenny

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Thursday, October 13, 2011 7:22 PM
To: Jeanine M. Swalec
Cc: Kelley, Laurie
Subject: RE: NDA 202067 cartoon and container label.

As soon as I receive the recommendation from our review team, I will inform you.

thanks,

Sulin

From: Jeanine M. Swalec [JSWA@Lundbeck.com]
Sent: Thursday, October 13, 2011 5:21 PM
To: Sun, Su-Lin
Cc: Kelley, Laurie
Subject: Re: NDA 202067 cartoon and container label.

Dear Sulin and Laurie,

Email received and I will share with my team. I also got your voicemail Sulin and will communicate to my team the concerns of the FDA regarding this issue.

I interpret today's request in that we have the option to [REDACTED] (b) (4) [REDACTED] (b) (4) Is this correct?

In the event a selection error is identified post approval, what regulatory action could the FDA impose?

Thank you in advance for clarification. I know we are both eager to resolve and check off as completed.

Jenny

From: Sun, Su-Lin <Su-Lin.Sun@fda.hhs.gov>

To: Jeanine M. Swalec
Cc: Kelley, Laurie <Laurie.Kelley@fda.hhs.gov>
Sent: Thu Oct 13 15:17:43 2011
Subject: NDA 202067 cartoon and container label.

Dear Jenny:

Below are our comment for your September 15, 2011 cartoon container submission:



If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
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/s/

SU-LIN SUN
10/14/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Monday, October 03, 2011 11:02 AM
To: JSWA@Lundbeck.com
Subject: NDA 202067 urgent information request
Importance: High

Dear Jenny:

Our review team has urgent information request (see below), please send the info via email to me first ASAP, also formally submit under NDA 202067.

In the study report of the study OV-1012 (page 70), you listed a table (Table#21) Titled Percent Reduction in Average Weekly Rate of Drop Seizures (Baseline Compared to First, Middle, and Last 4 Weeks of Maintenance Period) – MITT Population. We would like to have the same table for the completers only (i.e., the patients who have completed last 4 weeks (Weeks 12-15) of the maintenance period).

Please send us the dataset and SAScodes for producing the table#21 (i.e., the listed table in your study report) and also for producing the same table for the completers.

thanks,
Sulin

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/s/

SU-LIN SUN
10/04/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, October 06, 2011 3:32 PM
To: 'Jeanine M. Swalec'
Subject: NDA 202067 FDA urgent Information request

Importance: High

Dear Jenny:

Our review team has another urgent information request, please send the requested info to me as soon as possible (email me first, then officially submit).

We would like to have another table and it will be same as the Table#21, page 70 (study report of OV-1012) for the MITT patients after imputing missing SZs for the dropout patients using LOCF approach. That is, all of the MITT patients will be included in calculating SZ rates at First 4 weeks, Middle 4 weeks, and last 4 weeks

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
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SU-LIN SUN
10/06/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, September 29, 2011 1:54 PM
To: 'Jeanine M. Swalec'
Subject: RE: NDA 202067
Attachments: NDA 202067 Onfi--FDA proposed highlight-- 092911.doc

email will be fine.

Attached is the Division's proposed highlight section.

Will you also include your counter proposal for highlight section by COB 10/3/11? If not--can you let me know when will we expected your counter proposed highlight section.

thanks,

Sulin

From: Jeanine M. Swalec [mailto:JSWA@Lundbeck.com]
Sent: Thursday, September 29, 2011 6:20 AM
To: Sun, Su-Lin
Subject: RE: NDA 202067

Good morning Sulin,

We'll be able to send you Monday afternoon a track changes word doc. Please let me know if I should simply email it to you or submit formally to the NDA. Also, any idea when we should expect MG and Highlights comments so we are ready to respond promptly?

Thanks in advance! Jenny

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Monday, September 26, 2011 6:27 PM
To: Jeanine M. Swalec
Subject: RE: NDA 202067

:-)

Please send track changes word document for our counter proposed comments. If you accept our proposed comment, please accept the track changes.

thanks,

Sulin

From: Jeanine M. Swalec [mailto:JSWA@Lundbeck.com]
Sent: Monday, September 26, 2011 7:26 PM
To: Sun, Su-Lin
Subject: RE: NDA 202067

Thanks Sulin! Email received and we'll be sure to respond no later than COB Oct 3rd. Jenny

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Monday, September 26, 2011 5:29 PM
To: Jeanine M. Swalec
Subject: NDA 202067
Importance: High

Dear Jenny:

Attached document is the Division's proposed draft label for NDA 202067. As we discussed previously, MG and highlight section has not been reviewed by our review team yet. We will send you those sections as soon as the review has been completed. In addition, there will be several nonclinical PMRs, I will send the information to you as soon as our review team reach their decision.

Please send us your counter proposal as soon as possible, no later than COB on OCT 3, 2011.

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
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SU-LIN SUN
09/29/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Monday, September 26, 2011 6:29 PM
To: 'Jeanine M. Swalec'
Subject: NDA 202067

Importance: High

Attachments: NDA 202067 Onfi--FDA proposed draft label--track change version--092611.doc

Dear Jenny:

Attached document is the Division's proposed draft label for NDA 202067. As we discussed previously, MG and highlight section has not been reviewed by our review team yet. We will send you those sections as soon as the review has been completed. In addition, there will be several nonclinical PMRs, I will send the information to you as soon as our review team reach their decision.



NDA 202067
nfi--FDA proposed .

Please send us your counter proposal as soon as possible, no later than COB on OCT 3, 2011.

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
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Silver Spring, MD 20903
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Fax: 301-796-9842
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/s/

SU-LIN SUN
09/26/2011



NDA 020427
NDA 022006
NDA 202067

INFORMATION REQUEST

CERTIFIED MAIL
RETURN RECEIPT REQUESTED

Lundbeck, Inc
Attention: Jenny Swalec
Sr. Director, Global Regulatory Affairs
4 Parkway North, Suite 200
Deerfield, IL 60015

Dear Ms. Swalec:

Please refer to your New Drug Applications (NDAs) submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for:

Application	Drug Product	Dosage Form
NDA 020427	Sabril (vigabatrin)	Tablets
NDA 022006	Sabril (vigabatrin)	Powder for Oral Solution
NDA 202067	Onfi (clobazam)	Tablets

FDA investigators have identified significant violations to the bioavailability and bioequivalence requirements of Title 21, Code of Federal Regulation, Part 320 in bioanalytical studies conducted by [redacted] (b)(4).¹ The pervasiveness and egregious nature of the violative practices by [redacted] (b)(4) has led FDA to have significant concerns that the bioanalytical data generated a [redacted] (b)(4) from April 1, 2005 to June 15, 2010, as part of studies submitted to FDA in New Drug Applications (NDA) and Supplemental New Drug Applications (sNDA) are unreliable. FDA has reached this conclusion for three reasons: (1) the widespread falsification of dates and times in laboratory records for subject sample extractions, (2) the apparent manipulation of equilibration or “prep” run samples to meet pre-determined acceptance criteria, and (3) lack of documentation regarding equilibration or “prep” runs that prevented [redacted] (b)(4) and the Agency from determining the extent and impact of these violations.

¹ These violations include studies conducted by [redacted] (b)(4) specific to the [redacted] (b)(4).

Serious questions remain about the validity of any data generated in studies by (b) (4) (b) (4) during this time period. In view of these findings, FDA is informing holders of approved and pending NDAs of these issues.

The impact of the data from these studies (which may include bioequivalence, bioavailability, drug-drug interaction, specific population, and others) cannot be assessed without knowing the details regarding the study and how the data in question were considered in the overall development and approval of your drug product. At this time, the Office of New Drugs is searching available documentation to determine which NDAs are impacted by the above findings.

To further expedite this process, we ask that you inform us if you have submitted any studies conducted by (b) (4) (b) (4) during the time period of concern (April 1, 2005 to June 15, 2010). Please submit information on each of the studies, including supplement number (if appropriate), study name/protocol number, and date of submission. With respect to those studies, you will need to do one of the following: (a) re-assay samples if available and supported by stability data, (b) repeat the studies, or (c) provide a rationale if you feel that no further action is warranted.

Please respond to this query within 30 days from the date of this letter.

This information should be submitted as correspondence to your NDA. In addition, please provide a desk copy to:

Office of New Drugs
Center for Drug Evaluation and Research
10903 New Hampshire Avenue
Bldg. 22, Room 6300
Silver Spring, MD 20993-0002

If you have questions, contact your designated Regulatory Project Manager, at (301) 796-2250.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

JACQUELINE H WARE

09/15/2011

Signed for Dr. Russell G. Katz

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, September 06, 2011 11:58 AM
To: 'Jeanine M. Swalec'
Cc: Kelley, Laurie
Subject: NDA 202067 container and carton proposed comments

Importance: High

Dear Jenny;

Below are the proposed container labels and carton labeling (all sizes and strengths) from our review team



Please let us know whether you accept our proposed comments or provide us with your counter proposal comments.

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
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/s/

SU-LIN SUN
09/06/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, August 26, 2011 1:09 AM
To: 'Jeanine M. Swalec'
Subject: NDA 202067 urgent info request

Importance: High

Attachments: NDA 202067 Onfi---FDA proposed PI comments 082511.doc

Dear Jenny:

Attached document has the Division's comment for the dosing section of the proposed PI for NDA 202067 Onfi (clobazam) tablet. Please send your response to us as soon as possible, no later than COB on September 2, 2011.



NDA 202067
nfi---FDA proposed.

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
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/s/

SU-LIN SUN
08/26/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Saturday, August 13, 2011 11:00 AM
To: JSWA@Lundbeck.com
Subject: NDA 202067

Dear Jenny:

Our CSS reviewer has the following request for additional data regarding abuse /overdose:

In your submitted NDA 202067 (Integrated Summary of Safety, Section 12.2 Postmarketing data, page 257) a statement that there were 106 adverse reports that mentioned clobazam overdose or increased drug levels in the postmarketing data. The details were not provide for the majority of these cases.

CSS understands that the bulk of these cases involve the use of clobazam in combination with other substances or might not be classified as overdose cases. However, to assist on the characterization of the potential for abuse of clobazam, CSS requests you to submit detailed information about these 106 cases listed as overdose/alcohol, overdose/other drugs or just overdose/increased level. CSS is not requesting information regarding the 2 reports that you claimed that they are incomplete.

Please provide your reponse to us as soon as possible.
If you have any question, please feel free to contact me.

thanks,
Sulin

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/s/

SU-LIN SUN
08/14/2011

Sun, Su-Lin

From: Jeanine M. Swalec [JSWA@Lundbeck.com]
Sent: Thursday, July 07, 2011 11:18 AM
To: Sun, Su-Lin
Subject: RE: Today Tcon

Dear Sulin,

Based on your team's comments, we do not see the need to have our telecon at 11:30EST. Thank you for being able to provide this information prior to the telecon. We'll still be on stand-by for the IND 111404 telecon.

Thanks! Jenny

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Thursday, July 07, 2011 10:00 AM
To: Jeanine M. Swalec
Subject: Today Tcon
Importance: High

Dear Jenny:

Here is the Clin pharm response for today's Tcon.

Question to FDA: Based on the rationale above, does the Agency agree that an in vitro study to evaluate CYP2C8 and CYP2B6 induction potential by CLB or N-CLB can be conducted as a post-marketing commitment?

Clinical Pharmacology response:

It is acceptable to conduct an in vitro study evaluating the CYP2C8 and CYP2B6 induction potential by CLB and N-CLB as a Phase 4 commitment. It will be a Post-Marketing Requirement (PMR), not a Post-Marketing Commitment (PMC), as there may be unexpected risks of drug interactions due to the induction of CYP2C8 and 2B6. This PMR request will not delay the NDA approval decision as set by the PDUFA date (23 October 2011).

Please let us know whether you agree with our comment.
Do you still wish to have Tcon or cancel the Tcon.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
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Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
07/07/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Wednesday, June 22, 2011 12:02 PM
To: 'Jeanine M. Swalec'
Subject: RE: NDA 202067 (Request for In Vitro Study)
Importance: High

Dear Jenny:

Here are the comments from our review team for your May 9, 2011 response to our request for In Vitro Study:

[Response to evaluation of Inhibition Potential of CYP2B6 - acceptable](#)
[Response to evaluation of Induction Potential of CYP2B6 and CYP2C8](#)

Based on our review of the in vitro and in vivo study results in the NDA, we do not agree with your position that there is no induction of CYP3A4 by clobazam or N-CLB. The drug-drug interaction study with midazolam in humans shows that clobazam decreased midazolam AUC and Cmax by 27% and 24%, respectively, and increased those of hydroxymidazolam by greater than 4-fold and 2-fold, respectively. Therefore, the potential for a clinically relevant induction of CYP2C8 or CYP2B6 enzymes cannot be ruled out. We recommend that you conduct an in vitro study to evaluate CYP2C8 and CYP2B6 induction potential by clobazam and N-CLB. As previously advised, if you intend to have the study reviewed during this NDA review cycle, please provide us an estimated timeline for a submission of the final study report.

If you have any question please feel free to contact me.

thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20903
Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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From: Jeanine M. Swalec [mailto:JSWA@Lundbeck.com]
Sent: Tuesday, June 07, 2011 1:54 PM
To: Sun, Su-Lin
Subject: RE: NDA 202067 (Request for In Vitro Study)

Dear Sulin,

Can you provide any follow-up on our response to this FDA request? Is your review team satisfied with our response that no additional in vitro studies are necessary or should we expect additional feedback from your team on this issues?

Respectfully, Jenny

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Monday, May 09, 2011 11:54 AM
To: Jeanine M. Swalec
Subject: RE: NDA 202067 (Request for In Vitro Study)

Dear Jenny:

Yes, please submit your response officially. I forward your email to our review team, as soon as I received their recommendation, I will let you know.

thanks,

Sulin

From: Jeanine M. Swalec [mailto:JSWA@Lundbeck.com]
Sent: Monday, May 09, 2011 11:18 AM
To: Sun, Su-Lin
Subject: RE: NDA 202067 (Request for In Vitro Study)

Hi Sulin,

Please see our response below. Let me know if our response should be officially submitted to the NDA and when we should expect feedback from your team.

Respectfully, Jenny

Sponsor Response

Inhibition Potential of CYP2B6

An *in vitro* inhibitory study was conducted to evaluate the inhibition potential of CYP2B6 by clobazam and N-CLB. This study utilized 10 different isozymes which included CYP2B6 as well as CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2D6, CYP3A4, UGT1A1, UGT1A6 and UGT2B4. Results from this *in vitro* inhibition study showed no inhibition potential for any of the noted CYP450 isozymes by clobazam and N-CLB. The results of this study are contained in study report OVNC-9006 which was included in the original NDA 202067 (Sequence No. 0000).

Induction Potential of CYP2B6 and CYP2C8

For the reasons outlined below, Lundbeck proposes that *in vitro* studies to evaluate the induction potentials of CYP2B6 and CYP2C8 by clobazam and N-CLB are not required.

As described in the FDA 2006 Draft Guidance - Drug Interaction Studies, CYP3A appears to be sensitive to all known co-inducers. Therefore, to evaluate whether an investigational drug induces CYP1A2, CYP2C8, CYP2C9, CYP2C19, CYP2B6, or CYP3A, the initial *in vitro* induction evaluation may include only CYP1A2 and CYP3A. If *in vitro* studies indicate that an investigational drug does not induce CYP3A metabolism, then *in vivo* induction-based interaction studies of the investigational drug and concomitant medications eliminated by CYP2C/CYP2B and CYP3A may not be needed.

An *in vitro* induction study was conducted, to evaluate the induction potential of CYP1A2, CYP2C19,

CYP3A4 and UGT1A1 by clobazam and N-CLB. (OVNC-9007) The study report for OVNC-9007 was included in the original NDA 202067 (Sequence No. 0000).

Results from study OVNC-9007 showed that clobazam and N-CLB did not induce CYP3A4 at therapeutic plasma concentrations, instead the potential to induce CYP3A4 was only observed *in vitro* at suprathreshold plasma concentrations. Additionally, results from an *in vivo* drug-drug interaction study (OV-1023) conducted in healthy volunteers showed that midazolam's (CYP3A4 substrate) metabolism was not significantly affected (27% decrease in AUC) in the presence of 40 mg clobazam at steady-state, a finding which also confirms that no induction of the CYP3A4 isozyme by clobazam or N-CLB is occurring.

When analyzing the results of experiments to determine whether a drug induces an enzyme's activity, "based upon current knowledge of cellular mechanisms leading to CYP enzyme induction, if induction studies with a test drug confirm that it is not an inducer of CYP3A4 then it can be concluded that the test drug is also not an inducer of CYP2C8, CYP2C9, or CYP2C19." (FDA 2006 Draft Guidance - Drug Interaction Studies).

In summary, Lundbeck believes that the lack of CYP3A4 induction observed in both the *in vitro* and *in vivo* trials obviates the need to evaluate clobazam and N-CLB induction potential on the CYP2C8 and CYP2B6 isozymes.

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Monday, May 02, 2011 10:14 AM
To: Jeanine M. Swalec
Subject: NDA 202067
Importance: High

Dear Jenny:

Here is the request from our review team:

"It appears that there are no studies conducted to evaluate the inhibition potential of CYP2B6 and the induction potentials of CYP2B6 and 2C8 by clobazam and N-CLB. We recommend you conduct *in vitro* studies to address the above mentioned issues. If you intend to submit the study report during this NDA review cycle, please provide us an estimated timeline."

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20903
Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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APPEARS THIS WAY ON ORIGINAL

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/s/

SU-LIN SUN
06/22/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Wednesday, June 22, 2011 12:13 PM
To: 'Jeanine M. Swalec'
Cc: Kelley, Laurie
Subject: NDA 202067 initial Label and Labeling comments

Importance: High

Attachments: NDA 202067 Onfi RPM labeling format review 06212011.pdf; NDA 202067 Onfi--Label and Labling recommendations .pdf

Dear Jenny:

We did a preliminary format review for your proposed NDA 202067 PI--please see attachment # 1, Please resubmit your revised PI, no later than COB of July 15, 2011



NDA 202067 Onfi
RPM labeling f...

Also there are additional label and labeling review comments provided by our reviewers from Office of Surveillance and Epidemiology (OSE)



NDA 202067
Onfi--Label and Lab.

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
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4 Page(s) of Draft Labeling have been Withheld in Full as b4 (CCI/TS) immediately following this page

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/s/

SU-LIN SUN
06/22/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, June 17, 2011 1:52 PM
To: 'Jeanine M. Swalec'
Subject: NDA 202067 information request

Importance: High

Dear Jenny:

Below is the information request from our reviewer, please send your response no later than COB of 6/30/2011.

In the clobazam ISS, you submitted tables 4.2.5.5 and 4.2.5.6 that summarized incidence and prevalence of AEs for different time periods. The first time period category you presented in both tables was Day 1-179. Given that the incidence and prevalence was highest for many of these events during the Day 1-179 period, we think it would be helpful to look incidence and prevalence within shorter intervals following initiation of treatment.

We ask that you recalculate the incidence and prevalence as you did in tables 4.2.5.5 and 4.2.5.6, for the following intervals:

Days 1-7
Days 8-14
Days 15-21
Days 22-35
Days 36-49
Days 50-77
Days 78-179

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20903
Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
06/17/2011



NDA 202067

**PROPRIETARY NAME REQUEST
CONDITIONALLY ACCEPTABLE**

Lundbeck, Inc.
4 Parkway North, Suite 200
Deerfield, Illinois 60015

ATTENTION: Jenny Swalec
Senior Director, Global Regulatory Affairs

Dear Ms. Swalec:

Please refer to your New Drug Application (NDA) dated December 23, 2010, received December 23, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act for Clobazam Tablets, 5 mg, 10 mg, and 20 mg.

We also refer to your March 22, 2011, correspondence, received March 23, 2011, requesting review of your proposed proprietary name, Onfi. We have completed our review of the proposed proprietary name, Onfi and have concluded that it is acceptable.

The proposed proprietary name, Onfi, will be re-reviewed 90 days prior to the approval of the NDA. If we find the name unacceptable following the re-review, we will notify you.

If **any** of the proposed product characteristics as stated in your March 22, 2011, submission are altered prior to approval of the marketing application, the proprietary name should be resubmitted for review.

If you have any questions regarding the contents of this letter or any other aspects of the proprietary name review process, contact Laurie Kelley, Safety Regulatory Project Manager in the Office of Surveillance and Epidemiology, at (301) 796-5068. For any other information regarding this application contact the Office of New Drugs (OND) Regulatory Project Manager, Su-Lin Sun at (301) 796-0036.

Sincerely,

{See appended electronic signature page}

Carol Holquist, RPh
Director
Division of Medication Error Prevention and Analysis
Office of Medication Error Prevention and Risk Management
Office of Surveillance and Epidemiology
Center for Drug Evaluation and Research

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/s/

CAROL A HOLQUIST
06/06/2011



NDA 202067

INFORMATION REQUEST

Lunbeck Inc.
Attention: Jenny Swalec
Sr. Director, Global Regulatory Affairs
4 Parkway North Suite 200
Deefield, IL 60015

Dear Ms. Swalec:

Please refer to your new drug application (NDA) originally submitted on December 23, 2010, under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act for clobazam tablets.

We are reviewing the Chemistry, Manufacturing, and Controls sections of your submission and have the following comments and information requests. We request a prompt written response in order to continue our evaluation of your NDA.

1. What are the critical quality attributes of the product and how are they affected by the various manufacturing process parameters? Provide the supporting data for the proposed range of various in-process parameters including the following:
 - (i) Clarify why tablet hardness is monitored as FIO (for information only) only? Include appropriate limits for the hardness. Your proposed limits should demonstrate the link between tablet hardness and dissolution.
 - (ii) For the (b)(4) the in-process data sheet records the (b)(4) What is the target (b)(4)? What is its relationship with your (b)(4) and thus dissolution?
 - (iii) You have a final (b)(4) specification of (b)(4) (b)(4) Provide data such as effect of (b)(4) on tablet hardness and dissolution to support the proposed range.
 - (iv) Provide data to demonstrate that the product quality is not affected when manufactured at upper or lower end of the proposed in process range for (b)(4) mentioned in table 2, 3.2.P.3.3. Additionally, include a valid range for each process condition in the "in process data sheet" for the (b)(4) (b)(4)
 - (v) You have mentioned (ref. P.3.4) that you have investigated various process parameters in an experimental design to determine their effect on tablet dissolution. Provide details of such experiments along with conclusions drawn from these experiments.
2. Justify why your finished product specification (b)(4) (b)(4)

3. We understand that the drug substance is referenced to the DMF (b)(4). However, you need to provide your acceptance criteria of the drug substance along with your analytical methods and supporting validation data.
4. Provide USP <661> test results for the packaging components to be used to market the drug product in US.
5. We do not agree with your proposed dissolution limit. Based on the data provided, the lowest average dissolution data was (b)(4) from batches # 0800959, 0800960 which were not used in clinical studies. Batches used for the clinical studies (e.g. # 0701322) showed faster dissolution profile (average of (b)(4)). Therefore your proposed dissolution limit of (b)(4) is not acceptable. We suggest that you revise your dissolution limit based on the actual dissolution data used for clinical studies or provide in vivo PK data showing that lots with Q of (b)(4)% drug release in 45 min will be still bioequivalent to the clinical batches.

If you have any questions, call Teshara Bouie, Regulatory Project Manager, at (301) 796-1649.

Sincerely,

{See appended electronic signature page}

Ramesh Sood, Ph.D.
Branch Chief,
Division of New Drug Quality Assessment I
Office of New Drug Quality Assessment
Center for Drug Evaluation and Research

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/s/

RAMESH K SOOD
06/06/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, June 03, 2011 10:16 AM
To: 'Jeanine M. Swalec'
Subject: NDA 202067 FDA information request

Importance: High

Attachments: NDA 202067 Onfi -Clobazam information request--060311.pdf

Dear Jenny:

Attached document is the information request from our safety review team.



NDA 202067 Onfi
-Clobazam info...

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20903
Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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FDA information request
NDA 202067 Onfi (clobazam)

June 3, 2011

As part of our review of the clobazam NDA we have the following requests for additional information. We ask that you provide a response in 2 weeks.

During our review we noticed instances where coding of verbatim terms has resulted in apparent splitting of similar AEs into a number of different preferred terms, which can result in underestimation of the frequency for a particular event. For example, you have the following separate AE preferred terms for the apparently related events of somnolence, sedation, hypersomnia, lethargy, and depressed level of consciousness. We ask that you provide analyses that combine these somnolence-related events and calculate the frequency in the Phase II/III controlled trials and all Phase II/III trials. We also ask that you provide analyses that examine onset and duration of these events. We also request that you examine potential predictive factors for these events, including, but not limited to demographic factors, clobazam dose, relationship to clobazam dose changes, concomitant use of other medication(s) that increase somnolence, and any other relevant factors that you identify. We also ask that you review all preferred terms from the Phase II/III trials to look for other instances where similar events were coded to separate preferred terms, and provided updated frequencies based on recoding of any such events to a single event term.

The labeling for one or more of the benzodiazepines, and the core safety data sheets and foreign labeling that you provided for clobazam, identify (b) (4) (b) (4) as contraindications for use, but you do not include these in your proposed labeling for clobazam. Please explain your rationale for these omissions.

You propose stating that clobazam is contraindicated in patients with (b) (4) (b) (4). Please provide a summary of all cases of (b) (4) (b) (4) to clobazam that you have identified. Please also provide an estimate of the frequency of (b) (4) (b) (4) to clobazam.

In your submission, you identified subject 0017-7005 as a potential case of DRESS but state that medical review of the case concluded that it was not a case of DRESS. Please provide an explanation of why the medical reviewer felt that this was not a case of DRESS.

We ask for additional information about pneumonia events in clobazam treated subjects. In your analyses you provided information about the total number of pneumonia cases in the clobazam database. We ask that you summarize the time to onset from initiation of clobazam, and that you examine potential predictive factors for these events, including, but not limited to demographic factors, clobazam dose, relationship to clobazam dose changes, history of pneumonia, history of aspiration, history of swallowing difficulties. We ask that you also examine whether patients that experienced somnolence-related AEs (see above) or increased secretions/drooling AEs were at increased risk for developing

pneumonia. Lastly we ask that you identify the pneumonia cases that were temporally related to seizures.

In your ISS and 120 day safety update, you provided information about subject 0017-7028, a 5 year old with a DILI adverse event. We request the following information for this subject:

All concomitant drugs (dose, start and stop dates, whether they are known to be hepatotoxic, information on rechallenge or dechallenge). This should include all prescription and non-prescription medications including natural products.

Evaluation of nondrug causes: recent hepatitis A, B, C, D, and E serology; evidence for biliary obstruction; imaging study results; recent history of severe hypotension or congestive heart failure; other underlying viral disease including CMV and EBV.

Any and all supplemental information, including consultation reports, and special studies.

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/s/

SU-LIN SUN
06/03/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, May 27, 2011 11:58 AM
To: 'Jeanine M. Swalec'
Subject: Urgent information request NDA 202067

Importance: High

Attachments: NDA 202067--clin pharm request to the sponsor 052711.pdf

Dear Jenny:

Attached document is the information request from our Clin Pharm team, please send us your response no later than COB on June 10, 2011



NDA 202067--clin
pharm request...

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20903
Office: 301-796-0036
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Please refer to the dataset “ax_a_1_1.xpt” which was submitted for population PK analyses.

1. There are about 60 patients in the study of OV-1012 who have $crcl < 30$ (severe renal impaired patients) in your dataset. Here are a few examples of many.
 - ID=8044 : CLCR(variable name in the dataset)=0.758,
 - ID=8057 : CLCR=1.017

These values seem to be unusual. Please clarify.

2. There appears to be inconsistent in coding of genotype, compared to the dataset of genotyping data, “ad1axa1.sas7bdat”. Here are a few examples of many.
 - ID=1013, STD=1022: your coding for genotype is EM (GENO=1) but in the dataset of genotyping it is recorded as *1/*2, IM.
 - ID=1014, STD=1022: your coding for genotype is EM(GENO=1) but in the dataset of genotyping it is recorded as *1/*2, IM.

There are about 70 patients who have difference in genotype information between population PK dataset (ax_a_1_1.xpt) and genotyping dataset (ad1axa1.sas7bdat)

We listed only a few examples. Please check the submitted datasets and provide the response by June 10, 2011.

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/s/

SU-LIN SUN
05/27/2011

REQUEST FOR CONSULTATION

TO (Office/Division): OSE

FROM (Name, Office/Division, and Phone Number of Requestor): Corinne P. Moody, Science Policy Analyst, Controlled Substance Staff, (301) 796-3152

DATE
May 24, 2011

IND NO.

NDA NO.
202-067

TYPE OF DOCUMENT

DATE OF DOCUMENT
December 23, 2010

NAME OF DRUG
Clobazam

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG

DESIRED COMPLETION DATE
July 1, 2011

NAME OF FIRM: H Lundbeck AS

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS: CSS is requesting OSE to review foreign databases regarding the abuse, misuse and overdoses associated with Clobazam, including psychiatric adverse events, suicidal behavior and death. Attached is our list of MedDRA terms which you may use to search for the abuse related terms.

Background:

Clobazam was first approved in 1970 in Australia and since then has been marketed under the brand names Frisium and Urbanol, as an anxiolytic since 1975 and as an anticonvulsant since 1984. It is approved as an adjunctive treatment of epilepsy in over 80 countries. The current NDA 202-067 in DNP is for the indication of the treatment of Lennox-Gastaut syndrome which is characterized by multiple seizure types, predominantly of the tonic, atonic, and atypical absence variety and drop seizures.

SIGNATURE OF REQUESTOR
Corinne P. Moody, Science Policy Analyst

METHOD OF DELIVERY (Check one)
 DFS EMAIL MAIL HAND

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

CORINNE P MOODY
05/24/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Monday, May 02, 2011 11:14 AM
To: 'Jeanine M. Swalec'
Subject: NDA 202067

Importance: High

Dear Jenny:

Here is the request from our review team:

"It appears that there are no studies conducted to evaluate the inhibition potential of CYP2B6 and the induction potentials of CYP2B6 and 2C8 by clobazam and N-CLB. We recommend you conduct in vitro studies to address the above mentioned issues. If you intend to submit the study report during this NDA review cycle, please provide us an estimated timeline."

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
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Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
05/02/2011

Sun, Su-Lin

From: Jeanine M. Swalec [JSWA@Lundbeck.com]
Sent: Wednesday, April 27, 2011 10:49 AM
To: Sun, Su-Lin
Cc: Summers, Kelly
Subject: RE: NDA 202067

Dear Sulin,

We agree with no REMS being required for NDA 202067.

Respectfully, Jenny

From: Sun, Su-Lin [mailto:Su-Lin.Sun@fda.hhs.gov]
Sent: Monday, April 25, 2011 1:52 AM
To: Jeanine M. Swalec
Cc: Summers, Kelly
Subject: NDA 202067
Importance: High

Dear Jenny:

On December 23, 2010, in your NDA submission, you proposed a risk evaluation and mitigation strategy (REMS) for Onfi (clobazam) to ensure that the benefits of the drug outweigh the increased risks of suicidal thoughts and behavior. You proposed that your REMS include a Medication Guide and timetable for submission of assessments of the REMS.

You may be aware that on February 28, 2011, the Food and Drug Administration published a Federal Register notice concerning the availability of a draft FDA guidance entitled "Medication Guides — Distribution Requirements and Inclusion in Risk Evaluation and Mitigation Strategies (REMS)." In addition to discussing the FDA's policy on Medication Guide distribution, this draft guidance addresses the following two topics related to Medication Guides: the FDA's current thinking regarding when Medication Guides will be required as a component in a REMS program as well as procedures for sponsors to follow to request removal of a Medication Guide from a REMS.

In light of this draft Guidance, we do not think that is not necessary for the Medication Guide to be part of a REMS to ensure that the benefits of Onfi (clobazam) outweigh its risks. We do believe, however, that the Medication Guide is still necessary for patients' safe and effective use of Onfi (clobazam). The Medication Guide under review is being considered as part of labeling; if the NDA is approved, the Medication Guide would become a part of the approved labeling.

Please send me an email to acknowledge your agreement of "no REMS" for NDA 202067 Onfi (clobazam).

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209

10903 New Hampshire Ave
Silver Spring, MD 20903
Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
04/28/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, March 18, 2011 4:49 PM
To: Timothy M. Cunniff
Cc: 'Jeanine M. Swalec'
Subject: FDA request information for NDA 202067

Importance: High

Dear Mr. Cunniff:

Here is urgent information request from our Clin Pharm reviewers for NDA 202067:

- There are no data submitted in the application on pharmacokinetic evaluation of clobazam in severe renal impairment or ESRD subjects. We'd like to inquire if there exist any data, either from the sponsor-conducted studies or from literature, including studies for other indications as well, which address the impact of severe renal impairment/ESRD on clobazam PK and/or a safety profile. If so, please provide the data, an appropriate analysis and an integrated summary of results no later than COB on April 1, 2011.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20903
Office: 301-796-0036
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/s/

SU-LIN SUN
03/18/2011



NDA 202067

FILING COMMUNICATION

Lundbeck Inc.
Attention: Jenny Swalec
Sr. Director, Global Regulatory Affairs
Four Parkway North, Suite 200
Deerfield, IL 60015

Dear Ms. Swalec:

Please refer to your New Drug Application (NDA) dated December 23, 2010, received December 23, 2010, submitted under section 505(b) of the Federal Food, Drug, and Cosmetic Act, for Onfi (clobazam) oral tablets (5mg, 10mg, and 20mg).

We also refer to your additional submissions dated January 13, 2011, January 21, 2011, February 7, 2011, February 9, 2011, February 10, 2011, February 11, 2011, February 14, 2011, and February 18, 2011.

We have completed our filing review and have determined that your application is sufficiently complete to permit a substantive review. Therefore, in accordance with 21 CFR 314.101(a), this application is considered filed 60 days after the date we received your application. The review classification for this application is **Standard**. Therefore, the user fee goal date is October 23, 2011.

We are reviewing your application according to the processes described in the Guidance for Review Staff and Industry: Good Review Management Principles and Practices for PDUFA Products. Therefore, we have established internal review timelines as described in the guidance, which includes the timeframes for FDA internal milestone meetings (e.g., filing, planning, midcycle, team and wrap-up meetings). Please be aware that the timelines described in the guidance are flexible and subject to change based on workload and other potential review issues (e.g., submission of amendments). We will inform you of any necessary information requests or status updates following the milestone meetings or at other times, as needed, during the process. If major deficiencies are not identified during the review, we plan to communicate proposed labeling and, if necessary, any postmarketing commitment requests by September 23, 2011.

At this time, we are notifying you that, we have not identified any potential review issues. However, we have the following specific comments regarding abuse potential.

1. We have not identified any filing issues and have determined that no additional abuse potential studies are necessary, if C-IV scheduling for clobazam as a benzodiazepine is accepted by you.
2. We will review the information submitted under the Abuse Potential Assessment of your NDA and will request additional information if needed.
3. We remind you that a complete abuse potential assessment of a drug includes primary data, data analysis and a discussion of the following areas:
 - a. Chemistry (including the chemical similarity to other drugs of abuse and ability to extract the drug of abuse from the preparation)
 - b. Pharmacokinetics and pharmacodynamics (including all data on receptor binding)
 - c. Primary data from abuse potential studies in animals and humans
 - d. Adverse events in clinical studies related to abuse potential
 - e. Information and data related to abuse potential integrated summaries of safety and efficacy (ISS and ISE)
 - f. Information related to overdose
 - g. Prospective assessment of incidence of misuse, abuse, physical dependence/withdrawal syndrome, tolerance, diversion during clinical studies

Please note that our filing review is only a preliminary evaluation of the application and is not indicative of deficiencies that may be identified during our review.

REQUIRED PEDIATRIC ASSESSMENTS

Under the Pediatric Research Equity Act (PREA) (21 U.S.C. 355c), all applications for new active ingredients, new indications, new dosage forms, new dosing regimens, or new routes of administration are required to contain an assessment of the safety and effectiveness of the product for the claimed indication(s) in pediatric patients unless this requirement is waived, deferred, or inapplicable.

Because the drug product for this indication has orphan drug designation, you are exempt from this requirement.

If you have any questions, call Su-Lin Sun, PharmD, Regulatory Project Manager, at (301) 796-0036.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

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/s/

RUSSELL G KATZ
03/03/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Friday, February 18, 2011 10:48 AM
To: 'Jeanine M. Swalec'
Subject: NDA 202067

Dear Jenny:

Per our request, these are the comments and requests from our CSS review team for NDA 202067 Onfi (clobazam) tablet:

1. CSS did not identify any filing issues and no additional abuse potential studies are necessary, if C-IV scheduling for clobazam as a benzodiazepine is accepted by the Sponsor.
2. However we remind the Sponsor that when the NDA for this drug is submitted 21 CFR § 314.50 (5) (vii) requires an Abuse Potential Section with a proposal for scheduling with justification and all scientific data that form the basis of the proposal. If during the review CSS identifies any missing data or information, we will let you know.
3. The abuse potential assessment of a drug includes primary data, data analysis and a discussion of the following areas:
 - a. Chemistry (including the chemical similarity to other drugs of abuse and ability to extract the drug of abuse from the preparation)
 - b. Pharmacokinetics and pharmacodynamics (including all data on receptor binding)
 - c. Primary data from abuse potential studies in animals and humans
 - d. Adverse events in clinical studies related to abuse potential
 - e. Information and data related to abuse potential integrated summaries of safety and efficacy (ISS and ISE)
 - f. Information related to overdose
 - g. Prospective assessment of incidence of misuse, abuse, physical dependence/withdrawal syndrome, tolerance, diversion during clinical studies

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20903
Office: 301-796-0036
Fax: 301-796-9842

Reference ID: 2907747

Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
02/18/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, February 10, 2011 12:56 PM
To: 'Jeanine M. Swalec'
Subject: NDA 202067 LNCT-019 tumor Dataset

Importance: High
Sensitivity: Confidential

Dear Jenny:

Our reviewer would like to request clarification for your February 9, 2011 submission for LNCT-019 Tumor Dataset.

According to our reviewer the total number of animal (high dose group in male mice) should be 145: 60 (original group) 43 (added after 6 weeks) and 42 (added after 9 weeks). However, from your Feb 9, 2011 submission---it has 41 (original group) 19 (added after 6 weeks) and 42 (added after 9 weeks) = total 102 animals.

Per our reviewer, please provide explanation about those animals not included in the Feb 9, 2011 dataset.

Please send your response to us as soon as you can.

P.S. Please don't forget to officially submit the dataset for LNCT-020 which was sent to me electronically on Feb 3, 2011.

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20903
Office: 301-796-0036
Fax: 301-796-9842
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/s/

SU-LIN SUN
02/10/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Tuesday, February 08, 2011 10:02 AM
To: 'Jeanine M. Swalec'
Subject: NDA 202067 FDA request information

Importance: High
Sensitivity: Confidential

Dear Jenny:

Here is the information request from our QT review team:

For QT Clinical Study Report CV-1022, **please provide the QTcI correction factor (slope β) for each subject and update dataset adeg2.xpt with RR related variables included.**

A Double-Blind, Double-Dummy, Randomized, Parallel Trial in Healthy Subjects Assessing the ECG Effects of Clobazam Following a Therapeutic and Supratherapeutic Dose Compared to Placebo with Moxifloxacin as the Active Control”.

If you have any question, please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20903
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/s/

SU-LIN SUN
02/08/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Monday, February 07, 2011 9:59 AM
To: 'Jeanine M. Swalec'
Subject: Additional FDA requested info for NDA 202067

Importance: High
Sensitivity: Confidential

Dear Jenny:

The Division would like to request more information for NDA 202067 Onfi (Clobazam) tablet :

I. Carcinogenicity STAT : (LNCT-020)--rat carc study dataset:

Please resubmit the male mouse study dataset with separate high dose groups for LNCT-020 rat carc study dataset. Per our reviewer that he was not able to distinguish the two high dose groups from the dataset you sent to me on 2/3/2011.

II. CMC:

1. With regard to the description and composition of the drug product (Module 3.2.P.1) provide a comprehensive description of tablet appearance including shape (e.g., round, oblong, flat, beveled, etc.) and approximate dimensions. Similarly, revise the drug product appearance criteria in Module 3.2.P.5 to include tablet shape and size.
2. In Module 3.2.P.3 you have provided only a brief description of the manufacturing process. In accordance with 21 CFR § 314.50(d)(1)(ii)(c), provide copies off the proposed or actual master production record, including a description of the equipment, to be used for manufacture of a commercial lot of the drug product or a comparably detailed description of the production process.
3. With regard to manufacture of clobazam tablets, you have not provided data from development or engineering studies to support the proposed process control parameters and acceptance criteria.
4. Provide justification for designation of (b) (4)

Please submit the above requests as soon as possible (especially the carcinogenicity dataset resubmission request).

If you have any question , please feel free to contact me.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20903
Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
02/07/2011

REQUEST FOR CONSULTATION

TO (Office/Division): IRT-QT consult
attn: Devi Kozeli

FROM (Name, Office/Division, and Phone Number of Requestor):
Division of Neurology Products:
Russell Katz, MD, Director

DATE
02/04/2011

IND NO.

NDA NO.
202067

TYPE OF DOCUMENT
New NDA application

DATE OF DOCUMENT
12/23/2010

NAME OF DRUG
Onfi (clobazam) tablet

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG
Anticonvulsants

DESIRED COMPLETION DATE
August 1, 2011

NAME OF FIRM: Lundbeck, Inc

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

- | | |
|---|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> OTHER (SPECIFY BELOW): | |

III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

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| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

The network location is : \\cdsesub5\EVSPROD\NDA202067\202067.ENX
Day 45: Feb 6, 2011; Day 60: Feb 21, 2011; Day 74: March 7, 2011
Filing meeting date 1/26/2011 RM # 4270 (11:00AM -12:00noon)
Mid-cycle meeting date: 05/26/11 11:00-1PM (room 4201)
Wrap up meeting date: 08/25/11 2:00-4:00 pm (room 4201)
PDUFA goal date: Oct 23, 2011 **Orphan designation**
NME for Treatment of Lennox-gastaut Syndrome (LGS) for 2 years & older

SIGNATURE OF REQUESTOR
Sulin Sun, PharmD
Regulatory Project Manager
Division of Neurology Products
Phone: (301) 796-0036
Su-Lin.Sun@fda.hhs.gov

METHOD OF DELIVERY (Check one)

- DFS EMAIL MAIL HAND
x DARTS

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Reference ID: 2901520

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SU-LIN SUN
02/04/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Thursday, February 03, 2011 2:50 PM
To: 'Jeanine M. Swalec'
Subject: NDA 202067 FDA requested LNCT-020 dataset

Importance: High
Sensitivity: Confidential

Dear Jenny:

Our carcinogenicity stat reviewer is requesting the rata dataset for LNCT-020. Please send me electronically as soon as you can. Per our reviewer that dataset submitted for LNCT-020 with the original NDA submission was the same dataset for the mouseLNCT-019. Please also submit it officially.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20903
Office: 301-796-0036
Fax: 301-796-9842
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/s/

SU-LIN SUN
02/03/2011

Sun, Su-Lin

From: Sun, Su-Lin
Sent: Monday, January 31, 2011 11:57 AM
To: 'Jeanine M. Swalec'
Subject: NDA 202067 FDA requested Clin pharm info

Importance: High
Sensitivity: Confidential

Dear Jenny:

Here are the requested info from our clin pharm reviewer. Please send the 2nd bullet point requested info (highlighted in red color) as soon as possible to facilitate reviewing process.

- Please provide the QC validation reports for the legacy studies (e.g., LC-010). If they were submitted, please identify the location of the files.
- **We request you to make reference to each statement/conclusion in the Clinical Pharmacology and Biopharmaceutics Review Aid with the study number and a link to the study report. For example, most statements in the sections of 2.4.2.1 Absorption and 2.4.3. Mass balance are missing the study reference.**
- Please submit the genotype data used to assign CYP2C19 metabolic phenotypes.

Thanks,

Su-Lin Sun, PharmD
LCDR, United States Public Health Service

Regulatory Project Manager
Food and Drug Administration
Office of Drug Evaluation I – Division of Neurology Products
Bldg. 22, Room 4209
10903 New Hampshire Ave
Silver Spring, MD 20903
Office: 301-796-0036
Fax: 301-796-9842
Email: Su-Lin.Sun@fda.hhs.gov

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/s/

SU-LIN SUN
01/31/2011

REQUEST FOR CONSULTATION

TO (Office/Division): DB 6-- Division of Biometrics
Attn: Karl Lin, PhD.

FROM (Name, Office/Division, and Phone Number of Requestor):
Russell Katz, MD, Division of Neurology Products

DATE
January 25, 2011

IND NO.

NDA NO.
202067

TYPE OF DOCUMENT
New NDA application

DATE OF DOCUMENT
December 23, 2010

NAME OF DRUG
Onfi (clobazam) tablet

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG
anticonvulsants

DESIRED COMPLETION DATE
August 01, 2011

NAME OF FIRM: Lundbeck, Inc

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

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|--|---|
| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): New NDA (NME) application | |

III. BIOPHARMACEUTICS

- | | |
|--|--|
| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

- | | |
|--|--|
| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

- | | |
|-----------------------------------|--------------------------------------|
| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
|-----------------------------------|--------------------------------------|

COMMENTS / SPECIAL INSTRUCTIONS:

The network location is : \\cdsesub5\EVSPROD\NDA202067\202067.ENX

Day 45: Feb 6, 2011; Day 60: Feb 21, 2011; Day 74: March 7, 2011

Filing meeting date 1/26/2011 RM # 4270 (11:00AM -12:00noon)

Mid-cycle meeting date: 05/26/11 11:00-1PM (room 4201)

Wrap up meeting date: 08/25/11 2:00-4:00 pm (room 4201)

PDUFA goal date: Oct 23, 2011

Orphan designation

NME for Treatment of Lennox-gastaut Syndrome (LGS) for 2 years & older

SIGNATURE OF REQUESTOR

Sulin Sun, PharmD
Regulatory Project Manager
Division of Neurology Products
Phone: (301) 796-0036
Su-Lin.Sun@fda.hhs.gov

METHOD OF DELIVERY (Check one)

- DFS EMAIL MAIL HAND
x DARRTS

PRINTED NAME AND SIGNATURE OF RECEIVER

PRINTED NAME AND SIGNATURE OF DELIVERER

Reference ID: 2896550

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/s/

SU-LIN SUN
01/25/2011

REQUEST FOR CONSULTATION

TO (Office/Division): HFD-710 Division of Biometrics
Attn: Kun Jin, PhD

FROM (Name, Office/Division, and Phone Number of Requestor):
Russell Katz, MD, Division of Neurology Products

DATE
January 6, 2011

IND NO.

NDA NO.
202067

TYPE OF DOCUMENT
New NDA application

DATE OF DOCUMENT
December 23, 2010

NAME OF DRUG
Onfi (clobazam) tablets

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG
Anticonvulsants

DESIRED COMPLETION DATE
August 01, 2011

NAME OF FIRM: Lundbeck, Inc

REASON FOR REQUEST

I. GENERAL

- | | | |
|--|--|--|
| <input type="checkbox"/> NEW PROTOCOL | <input type="checkbox"/> PRE-NDA MEETING | <input type="checkbox"/> RESPONSE TO DEFICIENCY LETTER |
| <input type="checkbox"/> PROGRESS REPORT | <input type="checkbox"/> END-OF-PHASE 2a MEETING | <input type="checkbox"/> FINAL PRINTED LABELING |
| <input type="checkbox"/> NEW CORRESPONDENCE | <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> LABELING REVISION |
| <input type="checkbox"/> DRUG ADVERTISING | <input type="checkbox"/> RESUBMISSION | <input type="checkbox"/> ORIGINAL NEW CORRESPONDENCE |
| <input type="checkbox"/> ADVERSE REACTION REPORT | <input type="checkbox"/> SAFETY / EFFICACY | <input type="checkbox"/> FORMULATIVE REVIEW |
| <input type="checkbox"/> MANUFACTURING CHANGE / ADDITION | <input type="checkbox"/> PAPER NDA | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

II. BIOMETRICS

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| <input type="checkbox"/> PRIORITY P NDA REVIEW | <input type="checkbox"/> CHEMISTRY REVIEW |
| <input type="checkbox"/> END-OF-PHASE 2 MEETING | <input type="checkbox"/> PHARMACOLOGY |
| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
| <input type="checkbox"/> PROTOCOL REVIEW | <input type="checkbox"/> OTHER (SPECIFY BELOW): |
| <input checked="" type="checkbox"/> OTHER (SPECIFY BELOW): new NDA application | |

III. BIOPHARMACEUTICS

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| <input type="checkbox"/> DISSOLUTION | <input type="checkbox"/> DEFICIENCY LETTER RESPONSE |
| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

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| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

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| <input type="checkbox"/> CLINICAL | <input type="checkbox"/> NONCLINICAL |
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COMMENTS / SPECIAL INSTRUCTIONS:

The network location is : <\\cdsesub5\EVSPROD\NDA202067\202067.ENX>

Day 45: Feb 6, 2011; Day 60: Feb 21, 2011; Day 74: March 7, 2011

Filing meeting date 1/26/2011 RM # 4270 (11:00AM -12:00noon)

Mid-cycle meeting date: 05/26/11 11:00-1PM (room 4201)

Wrap up meeting date: 08/25/11 2:00-4:00 pm (room 4201)

PDUFA goal date: Oct 23, 2011

Orphan designation

NME for Treatment of Lennox-gastaut Syndrome (LGS) for 2 years & older

SIGNATURE OF REQUESTOR
Sulin Sun, PharmD
Regulatory Project Manager
Division of Neurology Products
Phone: (301) 796-0036
Su-Lin.Sun@fda.hhs.gov

METHOD OF DELIVERY (Check one)
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PRINTED NAME AND SIGNATURE OF RECEIVER
Reference ID: 2888023

PRINTED NAME AND SIGNATURE OF DELIVERER

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/s/

SU-LIN SUN
01/06/2011

REQUEST FOR DDMAC LABELING REVIEW CONSULTATION

****Please send immediately following the Filing/Planning meeting****

TO: CDER-DDMAC-RPM Michael Wade	FROM: (Name/Title, Office/Division/Phone number of requestor) Division of Neurology products Russell Katz, MD, director
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REQUEST DATE 1/6/2011	IND NO.	NDA NO. 202067	TYPE OF DOCUMENTS (PLEASE CHECK OFF BELOW)
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NAME OF DRUG Onfi (clobazam) tablet	PRIORITY CONSIDERATION	CLASSIFICATION OF DRUG Anticonvulsants	DESIRED COMPLETION DATE (Generally 1 week before the wrap-up meeting) August 01, 2011
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NAME OF FIRM: Lundbeck, Inc	PDUFA Date: October 23, 2011
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TYPE OF LABEL TO REVIEW

TYPE OF LABELING: (Check all that apply)	TYPE OF APPLICATION/SUBMISSION	REASON FOR LABELING CONSULT
<input checked="" type="checkbox"/> PACKAGE INSERT (PI)	xxx ORIGINAL NDA/BLA	<input checked="" type="checkbox"/> INITIAL PROPOSED LABELING
<input checked="" type="checkbox"/> PATIENT PACKAGE INSERT (PPI)	<input type="checkbox"/> IND	<input type="checkbox"/> LABELING REVISION
<input checked="" type="checkbox"/> CARTON/CONTAINER LABELING	<input type="checkbox"/> EFFICACY SUPPLEMENT	
<input checked="" type="checkbox"/> MEDICATION GUIDE	<input type="checkbox"/> SAFETY SUPPLEMENT	
<input checked="" type="checkbox"/> INSTRUCTIONS FOR USE(IFU)	<input type="checkbox"/> LABELING SUPPLEMENT	
	<input type="checkbox"/> PLR CONVERSION	

EDR link to submission:
The network location is : <\\cdsesub5\EVSPROD\NDA202067\202067.ENX>

Please Note: There is no need to send labeling at this time. DDMAC reviews substantially complete labeling, which has already been marked up by the CDER Review Team. The DDMAC reviewer will contact you at a later date to obtain the substantially complete labeling for review.

COMMENTS/SPECIAL INSTRUCTIONS: Day 45: Feb 6, 2011; Day 60: Feb 21, 2011; Day 74: March 7, 2011
Filing meeting date 1/26/2011 RM # 4270 (11:00AM -12:00noon)
Mid-cycle meeting date: 05/26/11 11:00-1PM (room 4201)
Wrap up meeting date: 08/25/11 2:00-4:00 pm (room 4201)
PDUFA goal date: Oct 23, 2011
Orphan designation
NME for Treatment of Lennox-gastaut Syndrome (LGS) for 2 years & older

SIGNATURE OF REQUESTER Sulin Sun, PharmD Regulatory Project Manager Division of Neurology Products Phone: (301) 796-0036 Su-Lin.Sun@fda.hhs.gov

SIGNATURE OF RECEIVER	METHOD OF DELIVERY (Check one) <input type="checkbox"/> eMAIL <input type="checkbox"/> HAND x DARTS
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Reference ID: 2887915

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/s/

SU-LIN SUN
01/06/2011

REQUEST FOR CONSULTATION

TO (Office/Division): **CSS**

FROM (Name, Office/Division, and Phone Number of Requestor):
Division of Neurology Products:
Russell Katz, MD, Director

DATE
1/6/2011

IND NO.

NDA NO.
202067

TYPE OF DOCUMENT
New NDA application

DATE OF DOCUMENT
12/23/2010

NAME OF DRUG
Onfi (clobazam) tablet

PRIORITY CONSIDERATION

CLASSIFICATION OF DRUG
Anticonvulsants

DESIRED COMPLETION DATE
August 1, 2011

NAME OF FIRM: **Lundbeck, Inc**

REASON FOR REQUEST

I. GENERAL

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| <input type="checkbox"/> MEETING PLANNED BY | <input type="checkbox"/> CONTROL SUPPLEMENT | |

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| <input type="checkbox"/> CONTROLLED STUDIES | <input type="checkbox"/> BIOPHARMACEUTICS |
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III. BIOPHARMACEUTICS

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| <input type="checkbox"/> BIOAVAILABILITY STUDIES | <input type="checkbox"/> PROTOCOL - BIOPHARMACEUTICS |
| <input type="checkbox"/> PHASE 4 STUDIES | <input type="checkbox"/> IN-VIVO WAIVER REQUEST |

IV. DRUG SAFETY

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| <input type="checkbox"/> PHASE 4 SURVEILLANCE/EPIDEMIOLOGY PROTOCOL | <input type="checkbox"/> REVIEW OF MARKETING EXPERIENCE, DRUG USE AND SAFETY |
| <input type="checkbox"/> DRUG USE, e.g., POPULATION EXPOSURE, ASSOCIATED DIAGNOSES | <input type="checkbox"/> SUMMARY OF ADVERSE EXPERIENCE |
| <input type="checkbox"/> CASE REPORTS OF SPECIFIC REACTIONS (List below) | <input type="checkbox"/> POISON RISK ANALYSIS |
| <input type="checkbox"/> COMPARATIVE RISK ASSESSMENT ON GENERIC DRUG GROUP | |

V. SCIENTIFIC INVESTIGATIONS

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COMMENTS / SPECIAL INSTRUCTIONS:

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Orphan designation

NME for Treatment of Lennox-gastaut Syndrome (LGS) for 2 years & older

SIGNATURE OF REQUESTOR
Sulin Sun, PharmD
Regulatory Project Manager
Division of Neurology Products
Phone: (301) 796-0036
Su-Lin.Sun@fda.hhs.gov

METHOD OF DELIVERY (Check one)
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Reference ID: 2887864

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/s/

SU-LIN SUN
01/06/2011



NDA 202067

NDA ACKNOWLEDGMENT

Lundbeck Inc.
Attention: Jenny Swalec
Sr. Director, Global Regulatory Affairs
Four Parkway North, Suite 200
Deerfield, IL 60015

Dear Ms. Swalec:

We have received your New Drug Application (NDA) submitted under section 505(b)(1) of the Federal Food, Drug, and Cosmetic Act (FDCA) for the following:

Name of Drug Product: Onfi (clobazam)
Oral tablets (5mg, 10mg, and 20mg)

Date of Application: December 23, 2010

Date of Receipt: December 23, 2010

Our Reference Number: NDA 202067

Unless we notify you within 60 days of the receipt date that the application is not sufficiently complete to permit a substantive review, we will file the application on February 21, 2011, in accordance with 21 CFR 314.101(a).

If you have not already done so, promptly submit the content of labeling [21 CFR 314.50(l)(1)(i)] in structured product labeling (SPL) format as described at <http://www.fda.gov/ForIndustry/DataStandards/StructuredProductLabeling/default.htm>. Failure to submit the content of labeling in SPL format may result in a refusal-to-file action under 21 CFR 314.101(d)(3). The content of labeling must conform to the content and format requirements of revised 21 CFR 201.56-57.

You are responsible for complying with the applicable provisions of sections 402(i) and 402(j) of the Public Health Service Act (PHS Act) [42 USC §§ 282 (i) and (j)], which was amended by Title VIII of the Food and Drug Administration Amendments Act of 2007 (FDAAA) (Public Law No, 110-85, 121 Stat. 904). Title VIII of FDAAA amended the PHS Act by adding new section 402(j) [42 USC § 282(j)], which expanded the current database known as ClinicalTrials.gov to include mandatory registration and reporting of results for applicable clinical trials of human drugs (including biological products) and devices.

In addition to the registration and reporting requirements described above, FDAAA requires that, at the time of submission of an application under section 505 of the FDCA, the application must be accompanied by a certification that all applicable requirements of 42 USC § 282(j) have been met. Where available, the certification must include the appropriate National Clinical Trial (NCT) numbers [42 USC § 282(j)(5)(B)].

You did not include such certification when you submitted this application. You may use Form FDA 3674, "Certification of Compliance, under 42 U.S.C. § 282(j)(5)(B), with Requirements of ClinicalTrials.gov Data Bank," [42 U.S.C. § 282(j)] to comply with the certification requirement. The form may be found at <http://www.fda.gov/opacom/morechoices/fdaforms/default.html>.

In completing Form FDA 3674, you should review 42 USC § 282(j) to determine whether the requirements of FDAAA apply to any clinical trial(s) referenced in this application. Please note that FDA published a guidance in January 2009, "Certifications To Accompany Drug, Biological Product, and Device Applications/Submissions: Compliance with Section 402(j) of The Public Health Service Act, Added By Title VIII of the Food and Drug Administration Amendments Act of 2007," that describes the Agency's current thinking regarding the types of applications and submissions that sponsors, industry, researchers, and investigators submit to the Agency and accompanying certifications. Additional information regarding the certification form is available at:

<http://www.fda.gov/RegulatoryInformation/Legislation/FederalFoodDrugandCosmeticActFDCAct/SignificantAmendmentstotheFDCAAct/FoodandDrugAdministrationAmendmentsActof2007/ucm095442.htm>. Additional information regarding Title VIII of FDAAA is available at: <http://grants.nih.gov/grants/guide/notice-files/NOT-OD-08-014.html>. Additional information for registering your clinical trials is available at the Protocol Registration System website <http://prsinformo.clinicaltrials.gov/>.

When submitting the certification for this application, **do not** include the certification with other submissions to the application. Submit the certification within 30 days of the date of this letter. In the cover letter of the certification submission clearly identify that it pertains to **NDA 202067**, submitted on December 23, 2010, and that it contains the FDA Form 3674 that was to accompany that application.

If you have already submitted the certification for this application, please disregard the above.

The NDA number provided above should be cited at the top of the first page of all submissions to this application. Send all submissions, electronic or paper, including those sent by overnight mail or courier, to the following address:

Food and Drug Administration
Center for Drug Evaluation and Research
Division of Neurology Products
5901-B Ammendale Road
Beltsville, MD 20705-1266

All regulatory documents submitted in paper should be three-hole punched on the left side of the page and bound. The left margin should be at least three-fourths of an inch to assure text is not obscured in the fastened area. Standard paper size (8-1/2 by 11 inches) should be used; however, it may occasionally be necessary to use individual pages larger than standard paper size. Non-standard, large pages should be folded and mounted to allow the page to be opened for review without disassembling the jacket and refolded without damage when the volume is shelved. Shipping unbound documents may result in the loss of portions of the submission or an unnecessary delay in processing which could have an adverse impact on the review of the submission. For additional information, please see <http://www.fda.gov/Drugs/DevelopmentApprovalProcess/FormsSubmissionRequirements/DrugMasterFilesDMFs/ucm073080.htm>.

If you have any questions, call me at (301) 796-0036.

Sincerely,

{See appended electronic signature page}

Su-Lin Sun, PharmD
Regulatory Project Manager
Division of Neurology Products
Office of Drug Evaluation I

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/s/

SU-LIN SUN
01/05/2011



DEPARTMENT OF HEALTH AND HUMAN SERVICES

Food and Drug Administration
Silver Spring MD 20993

IND 070125

MEETING MINUTES

Lundbeck Inc.
Attention: Jenny Swalec
Sr. Director, Global Regulatory Affairs
Four Parkway North, Suite 200
Deerfield, IL 60015

Dear Ms. Swalec:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i) of the Federal Food, Drug, and Cosmetic Act for Clobazam tablets.

We also refer to the meeting between representatives of your firm and the FDA on August 31, 2010. The purpose of the meeting was to discuss your proposed format and content for submission of an NDA in eCTD format for clobazam for the treatment of Lennox-Gastaut Syndrome (LGS).

A copy of the official minutes of the meeting is attached for your information. Please notify us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, call Su-Lin Sun, PharmD, Regulatory Project Manager at (301) 796-0036.

Sincerely,

{See appended electronic signature page}

Russell G. Katz, M.D.
Division Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure: Meeting Minutes



FOOD AND DRUG ADMINISTRATION
CENTER FOR DRUG EVALUATION AND RESEARCH

MEMORANDUM OF MEETING MINUTES

Meeting Type: Type B

Meeting Category: Pre-NDA

Meeting Date and Time: August 31, 2010 3:00 – 4:00PM EST

Meeting Location: White Oak Bldg# 22, Room 1309

Application Number: IND 070125

Product Name: Clobazam Tablets

Indication: Adjunctive treatment of seizures associated with treatment of Lennox-Gastaut Syndrome (LGS) in patients \geq 2 years of age

Sponsor/Applicant Name: Lundbeck Inc.

Meeting Chair: Russell Katz, MD, Division Director

Meeting Recorder: Su-Lin Sun, Pharm D

FDA ATTENDEES

Division of Neurology Products (DNP)

Russell Katz, MD, Division Director
Norman Hershkowitz, MD, Ph.D., Clinical Team Leader
Philip Sheridan, MD, Clinical Reviewer
Lois Freed, Ph.D., Supervisory Nonclinical Pharmacologist
Edward Fisher, Ph.D., Nonclinical Reviewer
Lori Love, MD, Ph.D., Lead Medical Officer (CSS)
Angela Men, MD, Clinical Pharmacology Team Leader
Ta-Chen Wu, Ph.D., Clinical Pharmacology Reviewer
Ohidul Siddiqui, Ph.D., Biostatistics Reviewer
Linda Ulrich, Orphan Drug Reviewer
Su-Lin Sun, Pharm D, Regulatory Project Manager

SPONSOR ATTENDEES

Lundbeck Inc.

Stephen M. Sagar, MD, Clinical and Medical
Christopher Silber, MD, Clinical and Medical
[REDACTED]^{(b) (4)}, Clinical and Medical (consultant)
[REDACTED] Clinical Operations (consultant)
Dwain Tolbert, Ph.D., Clinical Pharmacology
Mark Walzer, Ph.D., Nonclinical
Rebecca Drummond, Ph.D., Statistics
[REDACTED]^{(b) (4)}, Statistics (consultant)
Isabelle Lefebvre, BSc, RAC EU & US, Regulatory Affairs
Byron Scott, RPh, Regulatory Affairs
Jenny Swalec, BS, Regulatory Affairs
David Baran, BS, Clinical Operations
Tim Cunniff, PharmD, Regulatory Affairs
Stephen Gulyas, Ph.D., MBA, Statistics
Randy Owen, MD, MBA, Clinical and Medical
Henrik Troest, MSc, Corporate Project Management

1.0 BACKGROUND

Clobazam was first approved in 1970 in Australia (international birth date) and has also been approved for the treatment of anxiety and/or the adjunctive treatment of epilepsy in over 100 countries.

In the U.S., an IND was filed on 25 May 2005 by Lundbeck Inc. (Lundbeck) (formerly Ovation Pharmaceuticals); the company was notified by the Division of Neurology Products on 24 June 2005 that clinical studies with clobazam under IND 70,125 may proceed. A Type B, End of Phase 2 (EOP2) meeting was held with the Division on 09 May 2007 to discuss the results obtained from the completed Phase 2 study, OV -1002, and to discuss planning for clobazam Phase 3 development and preparation for filing a U.S. NDA.

Lennox-Gastaut syndrome (LGS) is estimated to represent 1 % to 2% of all childhood epilepsy cases. Therefore, LGS affects fewer than 200,000 people in the United States (US), and in accordance with Code of Federal Regulations (CFR) 21CFR 316.20, qualifies as an orphan indication.

On 24 August 2007, Lundbeck submitted an Orphan Drug Application requesting Orphan Drug Designation for clobazam, a 1,5 benzodiazepine, being developed for the adjunctive treatment of Lennox-Gastaut syndrome in patients 2 years of age and older. Orphan drug designation was awarded on 18 December 2007.

2. DISCUSSION

A. Regulatory:

Question 1: We believe that the robust, clinically meaningful, and statistically significant efficacy across all dosing for reduction of mean weekly drop attack seizure rates as demonstrated in the single pivotal Phase 3 randomized, double-blind, placebo-controlled, parallel group study (OV - 1012), supported by statistically significant efficacy results in the Phase 2 randomized, double-blind clinical study (OV-1002), are sufficient to proceed with NDA filing of clobazam as adjunctive therapy for the treatment of seizures associated with LGS.
Does the Agency agree?

Question 1 Rationale

All clobazam dose groups in Study OV-1012 were statistically significantly superior ($p < 0.05$) to the placebo group for mean percent reduction in average weekly rate of drop seizures from baseline to the maintenance period. When compared to placebo, the medium-dose and high-dose groups met the criterion for robust statistical significance ($p \leq 0.01$). Additionally, a statistically significant linear trend ($p < 0.0001$) of increasing efficacy with increasing dose was observed. Multiple sensitivity analyses were performed on the primary endpoint in order to assess the robustness of the outcome. These analyses confirm the primary analysis using rank-

transformed data, log-transformed data, and changes in imputation strategies. All sensitivity analyses yielded the same interpretation as the primary analysis; that is, clobazam is effective as adjunctive therapy in patients with LGS on a stable AED regimen. Section 4.3.4.2 Summary of Efficacy Results for Study OV-I012 provides a summary of the efficacy data from Study OV-I012 (page 76).

Based on the May 1998 FDA guidance for industry "Providing Clinical Evidence of Effectiveness for Human Drug and Biological Products", in certain circumstances, a single adequate and well-controlled study, without independent substantiation from another controlled study, can be relied upon for sufficient scientific and legal basis for approval.

As listed in the guidance, certain characteristics of a single adequate and well-controlled study could make the study sufficient support for an effectiveness claim. Study OV-1012 was designed with several of these characteristics. Study OV-1012 was a large multi-center study and is the largest study conducted to date in LGS patients, an orphan disease population.

Study results show that there is consistency across study subsets and the efficacy results were statistically robust for the medium and high dose regimen in reducing mean drop attacks compared to the placebo group. The low dose regimen achieved conventional statistical significance ($p < 0.05$).

Additionally, the Phase 2 Study (OV-I002) also serves as a supportive study and results from this study were also statistically very robust ($p \leq 0.01$). Section 4.3.4.3 Summary of Efficacy Results for Study 0 V -1002 provides a summary of the efficacy data from Study 0 V-I 002 (page 79).

Preliminary FDA Response:

At face, the Division agrees that the two studies (one pivotal and the other supportive) appear adequate for filing. However, considering the problem with tachyphylaxis observed for benzodiazepines, as expressed in our previous meeting, and the short duration of the studies (particularly the supportive study OV-1002) the issue of tolerance would have to be more thoroughly explored before the Division commits to this decision (see below).

Of course, the final decision as to whether such a study indeed supports efficacy can only be made upon review.

Discussion at Meeting: None.

Question 2: Clobazam has been marketed for over 30 years and in over 80 countries. We believe that this large safety experience, combined with data from our LGS clinical studies, provides adequate exposure to clobazam to enable a thorough evaluation of the safety of clobazam.

Does the Agency agree?

Question 2 Rationale

We believe that based on clobazam's extensive marketing history combined with the data generated from the Legacy Psychiatry studies and our Phase 1, 2, and 3 studies, there is sufficient exposure to clobazam to support submission and approval of the clobazam NDA for treatment of seizures associated with LGS, an orphan population. The table below displays the estimated patient exposure numbers to be included in the NDA.

Estimated Clobazam Exposure for the NDA

Duration of CLB Exposure	Number of Patients ¹
At least 1 dose	2203
6 months	379
12 months	232
24 months	94

¹1463 patients are from the legacy psychiatry studies and exposure rates are estimated

Preliminary FDA Response:

The numbers are adequate as per the ICH guidelines, but, in view of your description of this data, we are concerned about its quality and completeness. This will require discussion at the meeting. Moreover, are we to understand that there are a total of 2203 pts of whom 1463 are legacy psychiatry study patients with estimated exposure rates? Also, what safety information will be available from Study OV1004 at the time of the planned NDA submission (December 2010)?

Discussion at Meeting:

The Sponsor presented a PowerPoint presentation about the comprehensive safety database which is attached as an appendix to these meeting minutes. The Sponsor noted that the Legacy Epilepsy Study 301 and the Legacy Psychiatry Studies were conducted by a prior sponsor. Lundbeck retrospectively created an integrated safety database from CRFs (if available) or CSRs (if CRFs were not available). In the Legacy Psychiatry Studies, the degree of seriousness was not assigned to the adverse effects, but there were apparently no hospitalizations or deaths. The Agency asked for clarification concerning whether there were definitely no serious adverse effects or whether there was insufficient or missing data making it impossible to determine if there were serious adverse effects. The Agency asked the Sponsor to synthesize the laboratory data as best as can be done, even when this requires harmonizing the different units of measurements used by different laboratories for a particular laboratory parameter.

The Agency asked that copies of any publications based on these studies be included in the NDA submission.

Question 3: Given the available approved treatments for LGS and the robust efficacy and safety profile of clobazam, we are seeking to understand the Agency's perspective on the potential for both Fast Track and Priority Review or any mechanisms to preclude a standard 10 month review. This opinion will allow for greater clarity as to how to proceed with our application in order to provide a more targeted approach. Can the Agency provide its viewpoint on the possibility of both Fast Track and Priority Review with respect to clobazam based on the results of our LGS program?

Question 3 Rationale

Atonic and tonic seizures may cause sudden loss of posture and falls to the ground ("drop attacks"). These drop attacks lead to significant head trauma and necessitate the wearing of a protective helmet. Drop attacks, which may occur as a result of tonic, atonic or myoclonic seizures, are particularly disabling to patients with LOS, and indeed the falls pose a safety hazard to patients. These drop attacks occur in about 56% of patients who have slow spike and wave on ECG.

In the pivotal Phase 3 study (OV-1012), the percent reduction in the median average weekly rate of drop seizures from baseline to study end at the medium and high doses were 58% and 87%, respectively compared to a 23% median change in the placebo group. Comparatively to other drugs approved for the treatment of LGS, median percent change in tonic-atonic seizure frequency (drop attacks) over 28 days were reduced by Lamictal (34%) compared to placebo (9%) and median percent change in drop attacks reduced by Topamax (15%) compared to placebo (gain of 5%) according to approved labeling. Moreover, clobazam patients who were continuing to have frequent drop seizures after failing trials of multiple marketed AEDs had clinically meaningful responses to clobazam, documenting that clobazam addresses an unmet medical need.

There have been no studies conducted to compare the efficacy between clobazam and other LGS approved products for this orphan patient population. Given the small patient population, it would be exceedingly difficult to enroll sufficient numbers of patients to conduct a comparative study and we respectfully request that the Agency take this into consideration.

Preliminary FDA Response:

Reference to Agency's June 11, 2010 Deny Fast Track Letter indicates there is no clear evidence that clobazam demonstrates the potential to address unmet medical needs as detailed in FDA's Guidance for Industry (Fast Track Drug Development Programs- Designation, Development, and Application Review, January 2006). There is no direct within-study comparative evidence to suggest that clobazam is more effective than other approved therapies. Moreover, inter-study comparison suggests that one of the newer agents approved for Lennox Gastaut exhibits similar efficacy on face. Lastly, the actual numerical estimation of the magnitude of effect is only based upon a single placebo-controlled study. Therefore, clobazam will not qualify for a priority review. Any advice on priority review that the Agency provides during the pre-NDA meeting is tentative; the final determination will be made during the filing meeting once the NDA is submitted.

Discussion at Meeting: None

Question 4: Given the efficacy and safety profile of clobazam to be presented in the NDA, we seek to understand the Agency's viewpoint on whether an Advisory Committee meeting is likely to be needed to consider the approval of the product. It is clearly understood that issues which arise during NDA review may change your viewpoint on this matter.

Question 4 Rationale

Preparation for an Advisory Committee represents a significant investment of resources and forward planning on both the part of the Agency and the sponsor. It is clearly understood that if the NDA review generates unique safety or efficacy issues for clobazam, an opinion from the appropriate Advisory Committee will likely be sought. However, it is our understanding that new chemical entities which act by existing and well-established mechanisms, and which do not raise any unique safety or efficacy issues, do not generally require consideration by an Advisory Committee.

Preliminary FDA Response:

While we do not see a clear reason at the present time, the need for an Advisory Committee will be determined after the NDA is submitted and during the review process.

Discussion at Meeting: None

Question 5: As agreed to at the EOP2 meeting, clobazam is already scheduled under the CSS of 1970 as a Schedule iv product and our proposed labeling will include the standard language regarding abuse for benzodiazepine. As we do not intend to propose a change to the schedule of clobazam, no formal clinical abuse liability studies will need to be conducted for NDA approval. Does the Agency affirm that this agreement still stands?

Preliminary FDA Response:

It was agreed at the EOP2 meeting that formal abuse liability studies would not need to be submitted if the sponsor accepted standard language regarding abuse for benzodiazepines.

CSS Response:

- 1. If C-IV scheduling for clobazam as a benzodiazepine is accepted by the Sponsor, no additional abuse potential studies are necessary.**
- 2. We remind the Sponsor that when the NDA for this drug is submitted 21 CFR § 314.50 (5) (vii) requires an Abuse Potential Section with a proposal for scheduling with justification and all scientific data that form the basis of the proposal. The abuse potential assessment of a drug includes primary data, data analysis and a discussion of the following areas:**

- a. Chemistry (including the chemical similarity to other drugs of abuse and ability to extract the drug of abuse from the preparation)
- b. Pharmacokinetics and pharmacodynamics (including all data on receptor binding)
- c. Primary data from abuse potential studies in animals and humans
- d. Adverse events in clinical studies related to abuse potential
- e. Information and data related to abuse potential integrated summaries of safety and efficacy (ISS and ISE)
- f. Information related to overdose
- g. Prospective assessment of incidence of misuse, abuse, physical dependence/withdrawal syndrome, tolerance, diversion during clinical studies

3. Additionally CSS requests the updated receptor binding study and analysis of abuse-related adverse events and withdrawal symptoms from pooled previous clinical studies in adult patients using abuse-related MedDRA terms list provided by CSS.

For additional information, we refer you to the draft guidance: “*Guidance for Industry Assessment of Abuse Potential of Drugs*”, available on the Internet at:
<http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM198650.pdf>

Discussion at Meeting:

The Applicant plans to include requested Abuse Liability Assessment analyses in the ISS and is seeking agreement from FDA to conduct separate analyses for the LGS population and legacy psychiatry population. The Agency agrees and reminds the applicant that post marketing surveillance data will be important to look at.

B. Nonclinical

Question 6: Does the Agency agree with our proposal and methodological approach for submitting datasets for the 2 long-term carcinogenicity studies?

Question 6 Rationale

Due to the legacy nature of the two rodent carcinogenicity studies (finalized 24 October 1979), electronic tumor datasets (tumor.xpt) for these studies were not available and thus we have created electronic tumor data sets from the data listings contained within the study reports of

these two studies. Our proposal and methodological approach for creating these datasets is further explained in Section 4.2.5 Nonclinical Toxicology Summary (page 36).

Preliminary FDA Response:

Yes. However, there is concern that, due to the interpretation of findings necessary to develop the datasets, the information provided in the study reports may not be entirely consistent with the results of the statistical analysis. The study reports should be revised to clearly explain data decisions (e.g., how cause of death can now be determined, how time to tumor detection was calculated, how masses observed in-life were “matched up” with microscopic findings) and any differences in nomenclature. Summary and individual animal data should be provided as originally presented and as re-coded.

Discussion at Meeting:

The sponsor provided the following plan for submitting rodent carcinogenicity studies (Slide 19 of presentation):

“Rodent Carcinogenicity Studies...

- ***Provide original study report for each study which includes summary and individual animal data.***
- ***Provide additional report for each study***
 - ***Include data decisions and any nomenclature changes used to create datasets***
 - ***Update to statistical analyses***
- ***Provide electronic tumor dataset (tumor.xpt) for each study.”***

The Division agreed that this was a reasonable approach.

Question 7: Does the Agency agree that the nonclinical development program supports filing of an NDA in patients with LGS?
--

Question 7 Rationale

We have completed the specific nonclinical studies requested by the Agency at the pre-IND and EOP2 meetings. The addition of these studies to those conducted by the prior sponsor now comprises a complete nonclinical development program. Module 4 in the NDA Table of Contents found in Appendix 1 of this document lists all the nonclinical studies that have been conducted to support the development of clobazam.

Preliminary FDA Response:

On face, the nonclinical studies conducted appear adequate, except for uncertainty regarding safety testing of potential major circulating metabolites. Based on the information provided, it is not clear if there are any major circulating metabolites in humans. If so, nonclinical data would need to be provided to document that all major

circulating metabolites in humans have been adequately tested in the appropriate nonclinical studies.

Discussion at Meeting:

The Division noted that a major circulating metabolite is defined as one that accounts for at least 10% of total circulating drug-related material (cf. Guidance for Industry M3(R2) Nonclinical Safety Studies for the Conduct of Human Clinical Trials and Marketing Authorization for Pharmaceuticals January 2010 ICH Revision 1).

C. Clinical Pharmacology:

Question 8: We believe that [REDACTED] (b) (4) [REDACTED] Does the Agency agree?

Question 8 Rationale

During the EOP2 meeting, the Agency requested additional information about the metabolism and metabolites of clobazam, in particular detailed results of human mass balance studies. A summary of human mass balance and corresponding data were submitted to IND 70,125 Serial NO.247 on 07 November 2008. The summary and data included in our 07 November 2008 submission is included in this document in Section 4.3.3.5 Metabolism and Human Mass Balance (page 69). [REDACTED] (b) (4)

Preliminary FDA Response:

We do not agree. [REDACTED] (b) (4)

[REDACTED] (b) (4)
[REDACTED] (b) (4)
[REDACTED] (b) (4) **Please consider conducting a formal mass balance study to adequately assess the metabolic disposition of clobazam.**

Discussion at Meeting:

The Sponsor presented additional information, as cited below from the Sponsor's presentation slides:

* "Since then:

- ✱ Lundbeck Inc performed additional data interpretation on the original 14-C ADME study (1975, 39 mg, single dose N=3).
 - ✱ CLB and N-CLB AUC₀₋₂₄ were 8726 and 2173 ng hr/mL, respectively and similar to values observed in clinical study OV-1023 (N=18, 40 mg, 2009) of 8783 and 2623 ng hr/mL, respectively. Suggests values from radiolabeled study are accurate.
- ✱ Conducted an additional study that confirms the CLB metabolism profile at steady state concentration in plasma and urine (OV-1038, 2009), following 11-day of 60 mg BID administrations (N=11 CYP2C19 WT genotype and N=1 CYP2C19 poor metabolizer).
 - ✱ Metabolite ID performed on plasma (48 hours) and urine (168 hours)
 - ✱ Metabolite were identified by a combination of HPLC retention time, accurate mass and MS/MS fragmentation patterns
 - ✱ LC-MS and LC-MS/MS (Multiple Reaction Monitoring; MRM and Enhanced Product Ion; EPI) assays
- ✱ Similar conclusions were derived from the 14C-Clobazam, single dose administration (39 mg), and the multiple dose tolerability titration trial (60 mg BID, 11 days to SS):
 - Parent was extensively metabolized (<10% recovered intact in urine) to N-CLB which in turn was subsequently metabolized.
 - N-dealkylation (sum of N-CLB and subsequent metabolic products in urine) was the primary route of clobazam metabolism
 - N-CLB was the only major metabolite in circulation. OH-CLB and OH-NCLB < 5% of parent AUC
 - All other metabolites detected in plasma (n=17) represented individually <0.5% at all time points through 48 hr.
 - CLB and N-CLG AUCs from 1975 radiolabeled study consisted with 2009 study
 - A recovery of total radioactivity of 93% was achieved at 21 days in the original 14C-Clobazam 82% recovered in urine as metabolic products (primary elimination route); 11% feces. (14C-ADME only)
 - Published data CYP3A4/5 for clobazam metabolism (demethylation): CYP2C19 for N-CLB metabolism (hydroxylation)
- ✱ We believe that human mass balance and metabolic disposition of clobazam have been adequately characterized and that no significant new data regarding clobazam metabolic disposition will be obtained from a new mass balance trial.”

As information of this newly conducted study was not included in the submission, it is difficult to conclude that human mass balance and metabolic disposition of clobazam have been adequately characterized during the meeting. The Agency expressed concern for the reliability of the limited data in literature, the presented study design (e.g., limited numbers of subjects, dosing with food), and the implication for labeling.

The Sponsor also reported that a 50% increase in CLB exposure was observed via CYP3A4 inhibition in the presence of ketoconazole. The Agency stated that this information will be reviewed at the time of the submission of the NDA.

The Sponsor mentioned an internal White Paper on the impact of hepatic impairment on the PK of clobazam. No further discussion occurred on this point.

The Sponsor stated that they have the data for Extensive and Poor Metabolizers of CYP2C19 in Phase 1 studies that evaluate the impact of polymorphic genotypes on PK and metabolism of CLB and N-CLB.

Question 9: Does the Agency agree that the clinical pharmacology program supports filing of an NDA in patients with LOS?

Question 9 Rationale

In addition to providing clarification of the metabolism of clobazam, we were asked to conduct specific clinical pharmacology studies and enhancements to our Phase 3 study during the pre-IND and EOP2 meetings, respectively. These studies have been completed and are listed in Table 6 Table of All Clobazam Clinical Studies in this document (page 47).

Preliminary FDA Response:

- 1. The listed clinical pharmacology studies are sufficient to support the filing of an NDA, providing that the sponsor adequately addresses the following issues:**
 - **The need for the formulation bridging between the formulations used by the previous sponsor and those used in current studies and for marketing, especially if the information from previous studies is important to support the approval and labeling.**
 - **Based on your description, the bioanalytical methods in some of studies conducted by the prior sponsor will not be acceptable, especially if the information from previous studies is important to support the approval and labeling.**

- 2. The list of the studies conducted to address the drug-drug interaction potential is generally acceptable to support the NDA. However, the adequacy of the study designs and results of the studies, including population PK analysis, are subject to the NDA review. The sponsor should refer to the Agency's Guidance for Drug Interaction Studies for detailed recommendations. At the NDA stage, the sponsor should also provide justifications for the appropriateness of the doses and/or concentrations of the interaction drugs used for the in vivo and in vitro studies. The following clinical pharmacology related review issues should be addressed in support of the NDA and labeling:**
 - **Sufficiency of the hepatic impaired patients studied**
 - **Drug-drug interaction potential involving other important UGTs (such as UGT1A4 and UGT2B7 for lamotrigine) that are relevant to concomitant AEDs or other co-medications for the intent-to-treat patient populations. If UGT1A4 and UGT2B7 were not studied, we recommend that you conduct a drug-drug interaction study with lamotrigine in healthy volunteers.**
 - **In vivo drug-drug interaction study between clobazam and a pure, strong P-gp inhibitor, such as quinidine per the Agency's drug-drug interaction Guidance, in healthy volunteers since both CLB and N-CLB are substrates for P-gp.**
 - **Since cimetidine was reported in literature to inhibit the elimination of clobazam and N-clobazam, there is a need to address whether clobazam is a substrate for other transporters (such as OCT or OAT) based on its major elimination pathway.**

- **The need to evaluate the impact of race/ethnicity and/or polymorphic genotypes of CYP2C19 on PK and metabolism of CLB and N-CLB**

Discussion at Meeting:

The Sponsor proposed that a P-gp Substrate Study should be performed as a PMC/PMR at the NDA stage. The Agency agreed since it is not a filling issue. No discussion on other points at the meeting.

D. Clinical:

Question 10: Does the Agency agree that our proposed data for inclusion, methods, and analyses are sufficient to evaluate the development of tolerance to the efficacy of clobazam in patients with LGS?

Question 10 Rationale

During the EOP2 meeting, the Agency expressed concern for the potential for patients to develop tolerance to benzodiazepines, thus leading to a lack of long-term efficacy. To address this possibility, the maintenance Phase for the Phase 3 study (OV-1 012) was lengthened from 8 to 12 weeks. Section 4.3.4.4 Proposed Content and Format of Integrated Summary of Efficacy (page 81) in this document describes the criteria used to analyze tolerance and includes brief results when applying these criteria to Study OV-1012 data. Data from OV -1004 will also be used to determine tolerance. In addition to tolerance data from Studies OV - 1012 and OV - 1004, the ISE will also include a discussion citing published nonclinical and clinical data about tolerance to benzodiazepines and specifically about clobazam.

Preliminary FDA Response:

The Sponsor addresses the issue on page 82. The Sponsor notes that the time course of the development of tolerance has not been well studied but appears to occur within 3-4 months in the majority of cases. Although this was the case in the Schmidt study, other studies suggest a longer period up to 8 months. The Sponsor was asked at the EOP2 meeting to provide a justification for why 12 weeks would be an adequate time period to evaluate tolerance. This must be addressed in greater detail (taking into account the published literature on this issue) in the NDA submission.

Although there is inadequate detail to critique a final technique for examining tolerance, the Division has the same reservations as to the Sponsor's description of potential approaches. First, the Sponsor is not examining the complete time period; they compare the first 4 weeks to the first 8 weeks. Second, the 50% responder rates are being used as an endpoint. This constitutes a very small number of patients from the complete sample (6 to 8% of patients were responders in any group). Perhaps change in treatment effect over time for each patient would be a better measure. The Sponsor should examine whether

there is an adequate statistical way of examining this issue and what the sensitivity of such a method may be, i.e. what is the smallest detectable difference in effect size.

Discussion at Meeting:

The Division acknowledged that they misunderstood the proposed method of analysis over time. However, the Division still stressed that the analysis of the responder rate was inadequate. The Sponsor should use the general change in frequency for each patient over time, comparing changes for each individual patient to their baseline seizure frequency rates.

Question 11: We do not plan to pool data from our LGS studies in the ISE, but instead present by study. Does the Agency agree with this proposal?

Question 11 Rationale

We do not believe it would be informative to pool the data from the placebo-controlled Phase 3 study with data from the Phase 2 dose-ranging study. The study designs of the 3 Lundbeck-sponsored LGS studies are summarized in the table below. OV-1002 and OV-1012 each had a 4-week baseline period followed by a 3-week titration period. The protocol-specified duration of the maintenance period was 4 weeks for OV-1002 and 12 weeks for OV-1012. Thus, only efficacy data through Week 4 of the maintenance period could be feasibly compared between studies.

Although both studies included treatment groups for clobazam 0.25 mg/kg and 1.00 mg/kg, the absence of a placebo treatment group in OV - 1002 may have altered the dose-response curve relative to the placebo-controlled OV -1012.

For additional information, Appendix 2 of this document contains our proposed ISE data table shells.

Study #	Description	# Clobazam Patients	Total Daily Doses mg as BID (target)
OV-1002	Phase 2 double-blind, randomized, dose-ranging, parallel group study of CLB in LGS	68	0.25, 1 mg/kg 10,40 (maximum dose)
OV-1012	Phase 3 double-blind, randomized, placebo-controlled, parallel group study of CLB in LGS	179	0.25, 0.5, 1 mg/kg 10, 20, 40, placebo (maximum dose)
OV-1004	Phase 2/3 open-label extension study of OV- 1002 and OV-1012	267	Up to 2.0 mg/kg 80 (maximum dose)

Preliminary FDA Response:

It seems reasonable not to pool the data especially in light of tolerance which may not be manifest after 4 weeks of treatment (OV1002) but may be manifest after 12 weeks of treatment (OV1012).

Discussion at Meeting: None

Question 12: We intend to include in the NDA an ISE and not include Module 2.7.3 Summary of Clinical Efficacy. Does the Agency agree?

Question 12 Rationale

As outlined in Question Number 9, we propose to not pool data from LGS studies in the ISE. If the Agency agrees with our proposal to not pool, there would be little to no difference between the content of the ISE and Module 2.7.3.

Preliminary FDA Response:

This is acceptable.

Discussion at Meeting: None

Question 13: Does the Agency agree with our method of creating Study 301 safety datasets for inclusion in the NDA?

Question 13 Rationale

Legacy Study 301 was a randomized, double-blind, active-controlled, multi-center study of clobazam as monotherapy in pediatric patients with epilepsy (primarily complex-partial seizures (CPS)) conducted in Canada. Case report forms (CRFs) for all patients who participated in Study 301 are not available from the prior sponsor. Table 6 (page 47) describes Study 301 study design. CRFs were only provided to us for those patients that discontinued the study due to an AE or experienced an SAE. We have retrospectively created an electronic dataset of safety data from CRF source data, when available, supplemented with safety data from the CSR listings for those patients for whom CRFs are not available.

Additional Study 301 details can be found in Section 4.3.5.3 Other Studies to Support Safety in this document (page 87).

Preliminary FDA Response:

Study 301 is included on page 53 of Table 6. Study 301 had 235 patients age 2-16 years, none of whom had LGS but had partial seizures or only generalized tonic clonic seizures. This study is published in *Epilepsia*. 1998 Sep; 39(9):952-9. The abstract indicates that 119/235 received CLB, 78/235 received CBZ, and 38/235 received PHT.

The completeness and quality of safety data for the legacy study is not clear from the meeting package and should be discussed at the meeting.

Discussion at Meeting:

The methods of data collection for the Legacy Epilepsy Study 301 and the Legacy Psychiatry Studies were presented in the PowerPoint presentation. See response to question 2.

Question 14: Does the Agency agree with our proposal that we should not retrospectively assign seriousness to adverse events in the Legacy Psychiatry studies?

Question 14 Rationale

The Legacy Psychiatry studies were conducted in the 1970's at higher clobazam doses in adult patients before stringent regulatory criteria were developed for designating AEs as serious; thus SAEs were not collected. We have thoroughly reviewed the available data and there is no clear documentation to substantiate designating any events as meeting today's criteria for serious. We have thus concluded that no SAEs were reported, and we do not feel it is appropriate to "guess", since the data are not verifiable. Additional Legacy Psychiatry studies details can be found in Section 4.3.5.3 Other Studies to Support Safety in this document (page 87).

Preliminary FDA Response

See answer to Question 13.

Discussion at Meeting:

See response to question 2.

Question 15: Does the Agency agree with our proposal as to how the Legacy Psychiatry studies clinical laboratory results will be presented in the NDA?

Question 15 Rationale

In the 44 Legacy Psychiatry studies conducted at higher clobazam doses in adult patients, clinical laboratory abnormalities that were reported as AEs will be summarized as AEs. Laboratory results will be provided in a comprehensive dataset, but we do not plan to summarize laboratory results across these studies due to inter-study differences in original laboratory units and original laboratory normals, and inconsistent or incomplete collection of clinical laboratory parameters across studies. For example, a Comprehensive Metabolic Panel was rarely collected, and only 1 study (Study 190) collected creatinine levels. In other studies, not all parameters were collected and thus the chemistry laboratory profiles are incomplete or very sparse (< 5 parameters evaluated (see table below). We therefore believe that pooling and summarizing laboratory results may lead to misleading or inaccurate conclusions.

Hepatic laboratory results (when available) will be reviewed for identification of "Events and Clinical Laboratories of Special Interest" and a description of the findings will be reported in the ISS.

Extent of Clinical Chemistry Laboratories Reported in Legacy Psychiatry Studies

Group	Complete¹	Incomplete²	No Labs
Controlled Legacy Studies Conducted in English in US and Canada (N=8)	4	4	N/A
Controlled Rest of World Legacy (N=18)	0	7	11
Controlled Non-CRF Legacy (N=9)	7	N/A	2
Uncontrolled CRF Legacy (N=5)	0	3	2
Uncontrolled Non-CRF Legacy (N=4)	0	11	3

¹ Blood glucose, BUN, SGOT/AST, SGPT/ALT, alkaline phosphatase, total bilirubin, LDH, calcium, phosphorus, and uric acid.

² <5 of the above parameters reported

Preliminary FDA Response

It is very difficult to review safety data when it is not adequately synthesized. Every effort should be made to modify all data into a format that permits such a synthesis and allows a single global presentation and analysis (e.g. conversion of one unit to another). Such a conversion, however, should be transparent and provide enough information for the Division to recreate that same synthesis.

Discussion at Meeting:

See response to Question 2.

Question 16: Does the Agency agree with the proposed data displays and analyses outlined in the statistical analysis plan (SAP) for the ISS?

Question 16 Rationale

Appendix 4 in briefing document contains our proposed ISS SAP and table shells.

Preliminary FDA Response

This can be discussed at the meeting.

Discussion at Meeting: None

Question 17: Does the Agency agree with our proposed list of events and clinical laboratories of special interest identified in the ISS statistical analysis plan (SAP)?

Question 17 Rationale

We intend to review the database and summarize particular adverse events which include: pneumonia, seizures (new and/or worsening), blood dyscrasias, skin reactions, hepatotoxicity, cancers, suicidality, and withdrawal syndrome. These AEs were selected based on serious toxicities seen with typical AEDs, AEs on which the Agency has typically focused on, as well the pattern of AEs/SAEs (i.e. pneumonia) reported at a higher than anticipated frequency in LGS studies with clobazam. Table 26 contains additional details on the identified events and clinical laboratories of special interest and what data sources will be evaluated.

Preliminary FDA Response

Table 26 is on page 95. Data source D is not identified. Why aren't the psychiatry legacy studies included as data sources? And what data will be available from OV 1004 (the open label follow-up to OV 1002 and OV 1012)?

SUDEP and DRESS should also be specifically examined.

Discussion at Meeting: None

Question 18: A prior sponsor conducted many studies in the 1970's, and MS Word files are not available. We propose to submit these reports in legacy form as single image PDFs since the quality of the paper is insufficient to adequately create text based files via optical character recognition (OCR). Does the Agency agree with this proposal?

Preliminary FDA Response

Which studies specifically are being referred to? Single image PDFs are not easy to review.

Discussion at Meeting: Although not discussed at the meeting, the sponsor should attempt to submit these files in a searchable format. The Division and our electronic submissions group staff are available to consult with the sponsor in preparing the submission in searchable format.

Question 19: The original electronic datasets for the individual Legacy Psychiatry studies conducted by a prior sponsor are not available and have been retrospectively created. Thus, we propose to include in the NDA a single integrated analysis dataset containing safety data across all Legacy Psychiatry supportive safety studies rather than individual study level datasets. Does the Agency agree with this proposal?

Question 19 Rationale

The Legacy Psychiatry studies are intended to support only safety and not contribute to the evaluation of efficacy. Therefore, the safety data from the 44 studies were integrated into one dataset for incorporation into the ISS database.

Preliminary FDA Response

This is acceptable as long as there are identifiers in the data sets as to what trial patient data are derived from.

Discussion at Meeting: None

Question 20: We propose not to include in the NDA patient profiles for the clinical studies for which data tabulations will be in SDTM format. These studies include all Lundbeck-sponsored Phase 1, 2, and 3 studies. Does the Agency with this proposal?

Question 20 Rationale

Study level SDTM 3.1.2 converted data domains in Version 5 SAS transport files will be included in the NDA for the Lundbeck-sponsored Phase 1, 2 and 3 clinical studies. Current FDA Study Data Specifications within the eCTD Guidance state that if submitted data domains are presented in the SDTM format, patient profiles are not required. Therefore, we plan to only include patient profiles in the NDA for Legacy Study 301 and the 44 Legacy Psychiatry studies.

Preliminary FDA Response

This will be referred to our electronic submissions group.

Discussion at Meeting:

Please submit patient profiles for all clinical studies.

Question 21: A portion of the Legacy Psychiatry studies was conducted in foreign countries, and therefore non-English CSRs and/or CRFs are available as the original source. The CSRs and CRFs have been subsequently translated into English. However, we propose to only include the English-translated versions in the NDA. Does the Agency agree with this proposal?

Question 21 Rationale

The original reports have been translated by a qualified translation service and certificates have been provided to attest to the accuracy of translation. There seems to be little value to be gained by providing the foreign language reports.

Preliminary FDA Response

This is acceptable, but the Sponsor should be able to supply an original language CSR passage or CRF if requested by the Division during the NDA review.

Discussion at Meeting: None

Question 22: Does the Agency agree with our proposal for inclusion of various narrative formats in the NDA?

Question 22 Rationale

We plan to include traditional textual written narratives for those patients who died while on study, discontinued a study due to an AE, experienced an SAE, or had an event or clinical lab of special interest for all studies but the Legacy Psychiatry studies.

Due to the limited available information for the Legacy Psychiatry studies, we propose to provide narratives in a tabular format since there are little data to summarize and describe. Appendix 3 of this document includes a sample narrative in tabular format planned.

For events and clinical laboratories of special interest found within our pharmacovigilance database, we propose to provide the CIOMS form associated with the AE in lieu of a traditional text based or tabular based narrative. Appendix 3 of this document includes a sample narrative in tabular format.

Preliminary FDA Response

Assuming that the form in Appendix 3 represents the CIOMS form, this may be adequate, but we have concerns. Thus, upon our examination of Appendix 3, the form does not seem to indicate whether the patient discontinued for reasons of the reported event (elevation of hepatic enzymes) or if that event was considered serious. Moreover, no lab values are included (pertinent negatives must be included with pertinent positives). Also, examination of this form reveals that the data are presented in an ambiguous fashion; e.g. sometimes data is noted as being unavailable and other times a dash is presented, presumably having the same meaning. In conclusion the data must be presented in a way that is clinically meaningful, as complete as possible, and unambiguous. A thorough standard narrative should be included with the form if such information is available. The lack of complete safety data on patients is a weakness in the application.

Discussion at Meeting:

Narratives were requested concerning patient deaths, withdrawals, and serious adverse effects. Legacy epilepsy Study 301 has contemporaneous narratives. Narratives from the older Psychiatry Legacy Studies would be retrospective.

E. Statistical Analysis Plan (SAP) for Study OV-1012:

"Double-Blind, Placebo-Controlled, Efficacy and Safety Study of Clobazam (0.25, 0.5 and 1.0 mg/kg/day) in Patients with Lennox-Gastaut Syndrome".

Comment from Biostatistics

Instead of considering ANCOVA analysis on the percent change from baseline as the primary analysis, it is recommended to consider following Rank ANCOVA analysis as primary analysis. The rank ANCOVA includes the rank of average seizure frequency at 12-week maintenance period as dependent measure and treatment, center, and the rank of average 4-week baseline seizure frequency as the independent variables. The current proposed analysis might be considered as a sensitivity analysis. In addition, it is also important to do ANCOVA analysis on the log transformed frequency data as another sensitivity analysis.

Discussion at Meeting:

The sponsor agreed on the above comment at the meeting. There is no need to make any amendment to include the above comment. It is a review issue. The sponsor will report the above analyses in the study report.

3.0 ISSUES REQUIRING FURTHER DISCUSSION

None

4.0 ACTION ITEMS

None

5.0 ATTACHMENTS AND HANDOUTS

1. Abuse Potential Terms (09/2009 version)
2. Clinical Pharmacology and Biopharmceutics Review Aid
3. Sponsor's presentation slides IND 70125—Clobazam: Pre-NDA meeting 08/31/2010

Additional Clinical Pharmacology Comment:

We request that the sponsor provide the summary section as a review aid for the CPB reviewer. Outline of the summary section of the HPBIO section is provided. At the time of NDA submission the sponsor can use this template to write the summary of the Clinical Pharmacology and Biopharmceutics section of the NDA or provide it to the agency as a review aid. This summary section should be submitted electronically with appropriate hyperlinks to the relevant supporting data (Document is provided separately).

Attachment- The following list of terms provides a general guide of terms suggestive of abuse potential. This list has been compiled based on our experience to date and is not intended to be inclusive of all possible abuse related MedDRA terms.

Terms suggestive of abuse potential:

- EUPHORIA-RELATED TERMS:

Euphoric mood: euphoria, euphoric, exaggerated well-being, excitement excessive, feeling high, felt high, high*, high* feeling, laughter. (* Exclude terms that clearly are not related or relevant such as "high blood pressure," etc.)

Elevated mood: mood elevate, elation.

Feeling abnormal: cotton wool in head, feeling dazed, feeling floating, feeling strange, feeling weightless, felt like a zombie, floating feeling, foggy feeling in head, funny episode, fuzzy, fuzzy head, muzzy head, spaced out, unstable feeling, weird feeling, spacey.

Feeling drunk: drunkenness feeling of, drunk-like effect, intoxicated, stoned, drugged.
Feeling of relaxation: Feeling of relaxation, feeling relaxed, relaxation, relaxed, increased well-being, excessive happiness.

Dizziness: dizziness and giddiness, felt giddy, giddiness, light headedness, light-headed, light-headed feeling, lightheadedness, swaying feeling, wooziness, woozy.

Thinking abnormal: abnormal thinking, thinking irrational, wandering thoughts.

Hallucination (auditory, visual, and all hallucination types), illusions, flashbacks, floating, rush, and feeling addicted.

Inappropriate affect: elation inappropriate, exhilaration inappropriate, feeling happy inappropriately, inappropriate affect, inappropriate elation, inappropriate laughter, inappropriate mood elevation.

- SUBJECTIVE RESPONSE TERMS INDICATIVE OF IMPAIRED ATTENTION, COGNITION, MOOD, AND PSYCHOMOTOR EVENTS WHICH ARE OFTEN ASSOCIATED WITH DRUGS OF ABUSE):

Somnolence: groggy, groggy and sluggish, groggy on awakening, stupor.

Mood disorders and disturbances (mental disturbance, depersonalization, psychomotor stimulation, mood disorders, emotional and mood disturbances, deliria, delirious, mood altered, mood alterations, mood instability, mood swings, emotional liability, emotional disorder, emotional distress, personality disorder, impatience, abnormal behavior, delusional disorder, irritability.

Mental impairment disorders: memory loss (exclude dementia), amnesia, memory impairment, decreased memory, cognition and attention disorders and disturbances, decreased concentration, cognitive disorder, disturbance in attention, mental impairment, mental slowing, mental disorders.

Drug tolerance, Habituation, Drug withdrawal syndrome, Substance-related disorders

- *DISSOCIATIVE/PSYCHOTIC (TERMS OFTEN ASSOCIATED PCP, AND KETAMINE):*

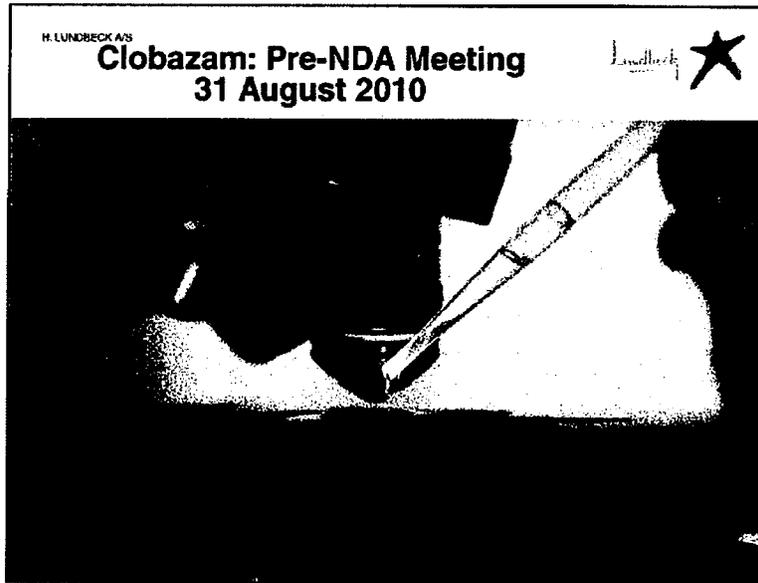
Psychosis: psychotic episode or disorder.

Aggressive: hostility, anger, paranoia

Confusion and disorientation: confusional state, disoriented, disorientation, confusion, disconnected, derealization, dissociation, detached, fear symptoms, depersonalization, perceptual disturbances, thinking disturbances, thought blocking, sensation of distance from one's environment, blank stare, muscle rigidity, non-communicative, sensory distortions, slow slurred speech, agitation, excitement, increased pain threshold, loss of a sense of personal identity.

APPENDIX

**PowerPoint Presentation from Lundbeck Inc. presented at the Pre-NDA Meeting
August 31, 2010**



Comprehensive Safety Database Exists

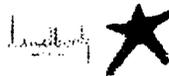
Lundbeck 

- * Safety in intended patient population
 - * 1002 + 1012 = 247 CLB exposures
 - * 1004 data
 - * ≥1 year data for N=190;
 - * ≥ 2 years data for N=94;
 - * ≥3 years for N=48;
 - * at least 4 years data for N=44
- * Safety in supportive patient population
 - * 301 data up to 1 year for N=65
 - * Legacy psychiatry studies
 - * Extensive Post-marketing
 - * Approved for nearly 40 years in over 80 countries
 - * 3.3 million patient exposures over the past 26 years

Estimated Clobazam Exposures (01 July 2010)				
Duration of CLB Exposure	Total*	LGS Studies	Study 301	Legacy Psy Studies
At least 1 dose	2203	267	119	1463
6 months	379	252	80	127
12 months	232	190	65	42
24 months	94	94	NA	NA

* Includes Phase 1 Studies

Legacy Epilepsy Study 301 and Legacy Psychiatry Studies
Question Nos. 2, 13, 14 and 15



- * Intended as supportive safety information
- * Not intended for labeling claims
- * Conducted by prior sponsor
 - * Psychiatry: Standards of the 1970s
 - * Study 301: 1990s similar to today's standards for clinical research
- * Conducted in multiple countries & languages
- * Placebo & active-controlled, uncontrolled
- * Integrated safety database retrospectively created by Lundbeck from CRFs (if available) and CSRs
 - * In Study 301, CRFs provided by prior sponsor for SAEs and withdrawals due to AEs; other safety data entered from CSRs
- * Adverse events often collected on symptom checklist rather than "spontaneous reports"
- * AE verbatim terms coded to current version of MedDRA

3

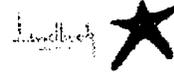
Legacy Epilepsy Study 301



- * Randomized, double-blind, double-dummy, active-controlled
- * Children with seizures (primarily CPS)
- * Clobazam monotherapy (N=119); n= 65 treated \geq 1 year
- * Multicenter (Canadian Study Group for Childhood Epilepsy)
- * Published in peer-reviewed journal (*Epilepsia* 1998)
- * Complete CSR to be submitted as supportive safety
- * AEs collected on:
 - * "Side Effect checklist"
 - * Specific CRF to collect spontaneously reported SAEs and AEs not listed on side effect checklist

4

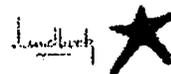
Legacy Psychiatry Studies



- * Conducted according to 1970s standards
- * Adult patients with variety of co-morbidities
- * Most were single center studies
- * Most studies ≤ 6 weeks in duration
- * Clobazam doses up to 60 and 80 mg/day
- * No standardized AE CRF across studies
 - * "checklist" vs spontaneous report
 - * may have resulted in over-reporting of "listed" terms
- * Seriousness was not assigned to AEs
- * No verifiable information to suggest any AE met today's criteria for serious

7

Legacy Psychiatry Studies

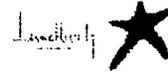


Legacy Study 310 Example

HEW NIMH
"Treatment-Emergent Symptoms"
Circa 1968

8

Human Mass Balance and Metabolic Disposition of Clobazam (Question No. 8)

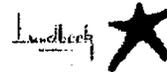


- * Similar conclusions were derived from the ¹⁴C-Clobazam, single dose administration (39 mg), and the multiple dose tolerability titration trial (60 mg BID, 11 days to SS):
 - Parent was extensively metabolized (<10% recovered intact in urine) to N-CLB which in turn was subsequently metabolized.
 - N-dealkylation (sum of N-CLB and subsequent metabolic products in urine) was the primary route of clobazam metabolism
 - N-CLB was the only major metabolite in circulation. OH-CLB and OH-NCLB < 5% of parent AUC
 - All other metabolites detected in plasma (n=17) represented individually <0.5% at all time points through 48 hr.
 - CLB and N-CLG AUCs from 1975 radiolabeled study consisted with 2009 study
 - A recovery of total radioactivity of 93% was achieved at 21 days in the original ¹⁴C-Clobazam 82% recovered in urine as metabolic products (primary elimination route); 11% feces. (¹⁴C-ADME only)
 - Published data CYP3A4/5 for clobazam metabolism (demethylation); CYP2C19 for N-CLB metabolism (hydroxylation)

- * We believe that human mass balance and metabolic disposition of clobazam have been adequately characterized and that no significant new data regarding clobazam metabolic disposition will be obtained from a new mass balance trial.

15

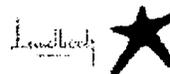
Tolerance to Clobazam (Question No.10)



- * Clarification of Background Document (p. 82)
 - * Our proposed OV-1012 analysis compares within treatment responders
 - * First 4 weeks to the final 4 weeks of maintenance period
 - * First 8 weeks to final 4 weeks of maintenance period.
 - * Uses data from entire maintenance period.
 - * About 60% of clobazam-treated subjects had >50% reduction in seizure frequency during maintenance period compared to baseline.
 - * Our analysis is based on the majority of subjects in OV-1012.

- * Duration of Study OV-1012
 - * There are no consistent reports in the literature regarding the time to development of tolerance for benzodiazepines
 - * Literature reports that the majority of patients appear to develop tolerance sooner than 3 months and therefore the OV-1012 clinical study is adequate to detect a signal and assess its overall importance to the long term efficacy.

18



Tolerance to Clobazam (Question No.10)

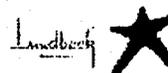
Table 26. Achieved Levels of Reduction from Baseline in Drop Seizures by Time in OV-1004 (MITT Population)

Month ¹	Subject Subsets			Total (N = n)
	6-month (N = n)	12-month (N = n)	24-months (N = n)	
Month 6, n (%)				
Discontinued study				
Any reduction	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
≥ 25% reduction				
≥ 50% reduction				
≥ 75% reduction				
100% reduction				
Month 9, n (%)				
Discontinued study				
Any reduction	XX (XX.X)	XX (XX.X)	XX (XX.X)	XX (XX.X)
≥ 25% reduction				
≥ 50% reduction				
≥ 75% reduction				
100% reduction				
Month 12, n (%)	Not Applicable			
Discontinued study				
Any reduction		XX (XX.X)	XX (XX.X)	XX (XX.X)
≥ 25% reduction				
≥ 50% reduction				
≥ 75% reduction				
100% reduction				

¹ Includes only subjects who achieved ≥ 50% reduction in drop seizures from baseline at Month 3. Subjects in the 6-month subset received their first dose of CLB ≥ 6 months but < 12 months before data cutoff for this submission. Subjects in the 12-month subset received their first dose of CLB ≥ 12 months but < 24 months before data cutoff. Subjects in the 24-month subset received their first dose of CLB ≥ 24 months before data cutoff.

² Reductions are from baseline. For subjects who received placebo in OV-1012, baseline corresponded to the first 7 non-missing diary days from OV-1012. For all other subjects, baseline was calculated from the last 7 non-missing diary days from the baseline period of the preceding study (OV-1002 or OV-1012).

17

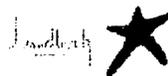


Statistics (FDA Comment E & Question No.16)

- * Study OV-1012 SAP FDA Comment
 - * Rank ANCOVA analysis as a sensitivity analysis & ANCOVA analysis on the log transformed frequency data have been completed
 - * Analyses will be included in CSR
- * ISS SAP and Data Displays
 - * Discuss FDA comments as requested in your preliminary responses

18

Other

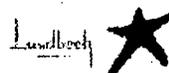


- ✕ P-gp Substrate Study (Question No. 9)
 - ✕ Propose as PMC

- ✕ Rodent Carcinogenicity Studies (Question No. 6)
 - ✕ Provide original study report for each study which includes summary and individual animal data
 - ✕ Provide additional report for each study
 - ✕ Include data decisions and any nomenclature changes used to create datasets
 - ✕ Update to statistical analyses
 - ✕ Provide electronic tumor dataset (tumor.xpt) for each study

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Other



- ✕ Abuse Liability Assessment (Question No. 5)
 - ✕ Plan to include requested analyses in ISS; seek agreement from FDA to conduct separate analyses for LGS population and legacy psychiatry population

- ✕ Patient Narratives (Question No. 22)
 - ✕ Traditional narratives except for legacy psychiatric studies provided in NDA. Legacy psychiatric studies will be tabular format, but will be inclusive of all data available. CIOMS instead of traditional text narratives for PM and will be inclusive of all data available

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This is a representation of an electronic record that was signed electronically and this page is the manifestation of the electronic signature.

/s/

RUSSELL G KATZ
11/09/2010



DEPARTMENT OF HEALTH & HUMAN SERVICES

Public Health Service

Food and Drug Administration
Rockville, MD 20857

IND 70,125

RECEIVED
JUL 11 2007

**OVATION
PHARMACUETICALS**

Ovation Pharmaceuticals, Inc.
Attention: Mahlaqa Patel, Sr. Manager
Global Regulatory Affairs
Four Parkway North
Deerfield, IL 60015

Dear Ms. Patel:

Please refer to your Investigational New Drug Application (IND) submitted under section 505(i)/505(b) of the Federal Food, Drug, and Cosmetic Act for clobazam tablets.

We also refer to the meeting between representatives of your firm and the FDA on May 9, 2007. The purpose of the meeting was to discuss your proposed Phase 3 study for the development of clobazam in Lennox-Gastaut Syndrome (LGS).

The official minutes of that meeting are enclosed. You are responsible for notifying us of any significant differences in understanding regarding the meeting outcomes.

If you have any questions, please call Tamy Kim, PharmD, Regulatory Project Manager, at (301) 1125.

Sincerely,

{See appended electronic signature page}

Russell Katz, MD
Director
Division of Neurology Products
Office of Drug Evaluation I
Center for Drug Evaluation and Research

Enclosure

MEMORANDUM OF MEETING MINUTES

Meeting Date: May 9, 2007
Location: White Oak, Bldg 22, Rm 1417
Application: IND 70,125
Sponsor: Ovation Pharmaceuticals, Inc.
Product & Use: Clobazam Tablets in Lennox-Gastaut Syndrome (LGS)
Type of Meeting: End-of-Phase 2
Meeting Chair: Russell Katz, MD
Meeting Recorder: Tamy Kim, PharmD

FDA Attendees

Russell Katz, MD, Neurology Division Director
John Feeney III, MD, Clinical Team Leader
Philip Sheridan, MD, Clinical Reviewer
Lois Freed, PhD, Supervisory Pharmacologist
Edward Fisher, PhD, Pharmacology Reviewer
Ta-Chen Wu, PhD, Clinical Pharmacology Reviewer
Atul Bhattaram, PhD, Pharmacometrics/Clinical Pharmacology Reviewer
Kun Jin, PhD, Supervisory Statistics Reviewer
Ohidul Siddiqui, PhD, Statistics Reviewer
Corinne Moody, Science Policy Analyst, Controlled Substance Staff
Tamy Kim, PharmD, Regulatory Project Manager

Sponsor Attendees

Stephen Collins, MD, PhD – Clinical and Medical
Katherine Tracy, MD, PhD – Clinical and Medical
Stephen Wanaski, PhD – Clinical and Medical
Bob Anders, PharmD – Clinical and Medical
Jason Bradt, MD, MBA, MHA – Clinical and Nonclinical Pharmacology
Radhi Abdalnabi, PhD – Statistics
Mahlaqa Patel, BA – Manufacturing and Development
Tim Cunniff, PharmD – Regulatory
Tom Stothoff, BA – Regulatory
Mike Rice, PhD – Regulatory
Jenny Swalec, BS – Regulatory

Background

The Sponsor requested feedback on their proposed Phase 3 study to evaluate clobazam in patients with LGS.

The questions discussed below were submitted as part of an End-of-Phase 2 meeting package dated April 9, 2007. The Sponsor's questions are presented in bold print followed by the preliminary FDA response in italic print (conveyed to the Sponsor by e-mail on May 8, 2007), and then a summary of the discussion during the meeting.

**SPONSOR QUESTIONS, FDA PRELIMINARY RESPONSES,
& SUMMARY OF MEETING DISCUSSION**

CLINICAL

Question 1: Does the Division agree with the design of the proposed Phase III study (study OV-1012), including the proposed endpoints and planned statistics (specifically, the planned primary efficacy analysis to be performed on the modified ITT population)?

FDA Preliminary Response:

Clinical

Overall, the study design is acceptable. One remaining concern is the tendency for patients to develop tolerance to benzodiazepines leading to lack of long-term efficacy. In a recent review, Dieter Schmidt estimated the development of tolerance for Clobazam to be "in as many as 50% of patients within weeks or months." A longer maintenance dosing period (e.g. 12 weeks rather than 8 weeks) could address this concern.

Statistics

It is recommended to drop the 'Center-by-Treatment' interaction from the primary ANCOVA model. The interaction needs to be evaluated in the secondary analysis, and should be reported. If it is statistically significant, then further exploratory analysis needs to be done to find the centers for which the interaction term becomes significant.

Meeting Discussion:

The Sponsor agreed with the Agency's preliminary comments and inquired specifically whether the modified ITT population was acceptable. The Agency stated that the modified ITT population would be acceptable.

The Agency had additional concerns about the period of risk for developing tolerance with the use of clobazam in LGS, and stated that the study should be performed long enough to adequately assess this tolerance phenomena. To address tolerance, it was suggested that the Phase 3 study be extended from 8 weeks to 12 weeks for maintenance treatment. In addition, the Sponsor should justify why the study length of 12 weeks is a sufficient duration to address tolerance. The Sponsor suggested that open-label data where patients were treated with clobazam for 9 months could be used to assess tolerance by evaluating patients in which clobazam was no longer efficacious. The Agency questioned this approach asking the Sponsor how they would determine that clobazam was losing efficacy in patients, since efficacy may fluctuate in patients. The Agency also inquired whether the study could be conducted longer than 12 weeks, and whether there was reliable data that distinguished the level of tolerability that develops when taking clobazam. The Sponsor stated that a one-

year study (N=235) comparing clobazam, carbamazepine, and phenytoin, using time to discontinuation as the primary endpoint demonstrated low tolerance for all three products. The Sponsor will need to make a compelling argument on this point.

Question 2: Does the Division agree with the proposed dose-selection rationale for study OV-1012?

FDA Preliminary Response:

Clinical Pharmacology

The choice of 3 doses levels (0.25, 0.5 and 1 mg/kg) are acceptable based on evidence from a Phase 2 study where a high dose 1 mg/kg (up to a total daily dose of 40 mg) was compared to a low dose of 0.25 mg/kg (up to a total daily dose of 10 mg). However, there are issues that you need to clarify:

You have proposed that patients in the planned trial will be placed in 1 of 6 weight groups as shown below. The reviewer calculated the approximate total daily dose (to be given BID) for each weight group.

Weight Group Dose	12.5-17.5	17.6-22.5	22.6-27.5	27.6-32.5	32.6-37.5	37.6+
0.25 mg/kg	3.1-4.3 (mg)	4.4-5.6 (mg)	5.6-6.8 (mg)	6.9-8.1 (mg)	8.1-9.3 (mg)	10 (mg)
0.5 mg/kg	6.2-8.7 (mg)	8.8-11.2 (mg)	11.3-13.7 (mg)	13.8-16.2 (mg)	16.3-18.7 (mg)	20 (mg)
1 mg/kg	12.5-17.5 (mg)	17.6-22.5 (mg)	22.6-27.5 (mg)	27.6-32.5 (mg)	32.6-37.5 (mg)	40 (mg)

You plan to use only one tablet strength of 5 mg in the clinical trial. Due to the availability of only one dose strength in the planned study, it is recommended that you simplify the dosing table as shown below:

Weight Group Dose	<= 30 kg	> 30 kg
0.25 mg/kg	5 (mg)	10 (mg)
0.5 mg/kg	10 (mg)	20 (mg)
1 mg/kg	20 (mg)	40 (mg)

Based on the final population pharmacokinetic model that would be developed it would be possible to further adjust the doses if needed by body-size.

Meeting Discussion:

The Sponsor agreed with the Agency's preliminary responses and there was no further

discussion of this question at the meeting.

Question 3: Does the Division agree that the safety and efficacy data from the Phase II and III LGS studies in conjunction with the additional safety and efficacy data described below provides sufficient exposures to clobazam for NDA filing?

FDA Preliminary Response:

Review of pages 32-36 does not indicate clearly how many long-term exposure patients as opposed to short-term will be providing data.

Meeting Discussion:

The Sponsor presented data from a Canadian Monotherapy trial, stating that this trial could add more safety data. According to the Sponsor's presentation on patients with LGS in the Canadian Monotherapy trial, 248 patients would be exposed to clobazam short-term, 202 patients would be exposed for > 6 months, and 159 patients would be exposed for > 12 months. For patients with epilepsy, ~367 patients would be exposed to clobazam short-term, ~272 patients would be exposed for > 6 months and ~249 patients would be exposed for > 12 months. Also, the Sponsor stated that they have safety data (in case report form) for the use of clobazam in patients with anxiety disorders.

The Agency suggested categorizing the safety and efficacy data for patients to < 12 years old and > 12 years old. However, the Sponsor responded that the study population > 13 years old was only approximately 20% of the study population. The Agency asked for the total number of patients with seizures between 2 and 6 years of age. The Sponsor responded that 36 to 40% of the patient population in their Phase 2 study was between that age range.

The Agency inquired about the prevalence of LGS in the US, and the Sponsor replied that the prevalence was ~14,000. The Office of Orphan products stated that the prevalence of LGS in the US has also been reported to be between 23,000 and 75,000 people.

Question 4: Does the Division agree that the single adequate and well-controlled study OV-1012 will support NDA approval of clobazam as add-on therapy for patients with LGS, provided that the results for the primary efficacy measure are statistically significant and there is consistency in the right direction across the majority of the secondary efficacy measures?

FDA Preliminary Response:

The Phase II OV-1002 study and the proposed Phase III Study OV-1012 together could support NDA approval if results are convincing.

Meeting Discussion:

The Agency stated that the Phase 2 study was shorter in length than what would

typically be acceptable. Therefore, in order for the Agency to accept the single Phase 3 study, the Phase 3 study should be longer in duration and the design robust. However, the acceptability of a single trial would also depend on the results of the trial.

The Agency also recommended that the sponsor explore exposure-response relationships on the secondary efficacy endpoints.

Question 5: Does the Division agree to Ovation's proposed content for the Integrated Summary of Safety in the NDA?

FDA Preliminary Response:

See answer to Question 3.

Meeting Discussion:

Please refer to meeting discussion under Question 3.

CLINICAL PHARMACOLOGY

Question 6: Does the Division agree that the metabolism of clobazam has been adequately characterized?

FDA Preliminary Response:

Clinical Pharmacology

We still need additional information about the metabolism and metabolites of clobazam, in particular:

- *The activity of the metabolites, metabolic enzymes involved and contributions of respective metabolic pathways of the active species.*
- *Results of human mass balance studies in detail should be provided or better summarized to assess the metabolic profile of clobazam, which will facilitate the decision making for any additional in vitro/in vivo evaluation and/or studies in special populations.*

Meeting Discussion:

The Sponsor presented information on the metabolic pathway of clobazam, and stated that its metabolites have been identified and are well-characterized. The Sponsor expressed that metabolic information is available in literature and presented results of a human mass balance study from one publication to indicate the contributions of various metabolites excreted into the urine (highest ~45% for M5; ~10% for M9). The Sponsor felt that the human mass balance has been well-characterized and the available information should address the Agency's concern. The Agency questioned whether the published human mass balance results (one publication), as presented by the Sponsor, was considered well-characterized.

The Sponsor agreed to provide more comprehensive information and justification in future submissions. The Agency stated that the need for any additional studies will depend on information provided by the Sponsor. The Agency also pointed out the discrepancy in the submission regarding the reported metabolite (i.e., M9) excreted in urine and commented on the need for study in renal impairment. The Sponsor clarified that the active metabolite, M9, is renally excreted.

Question 7a: Does the Division agree with the sponsor's assessments of the completed in vitro drug-drug interaction studies, the planned in vivo drug interaction study with ketoconazole (inhibition) and population PK analysis plans for Phase III as described above?

FDA Preliminary Response:

Clinical Pharmacology

1. Drug-drug interaction studies:

We do not agree with your conclusion

(b) (4)

Therefore, we still believe that there is a possibility of interaction in this case. You should at least consider an in vivo drug-drug interaction study to evaluate the potential impact of N-CLB on CYP2C9 activity. If, however, substrates of these enzymes are likely to be included as comedications in the proposed clinical trials, you may address this drug interaction through population analysis.

You should evaluate whether CLB and/or N-CLB are substrates or inhibitors of P-glycoprotein. We agree that there is a lack of CYP3A4 induction, therefore investigation for induction potential for P-glycoprotein will not be necessary.

We recommend that you conduct the ketoconazole drug-drug interaction study using a ketoconazole dose of 400 mg/day to maximize the inhibition potential, according to the Agency's Guidance.

You should plan for an in vivo drug interaction study with CYP2C19 inhibitor (e.g., omeprazole) in view of the extensive involvement of CYP2C19 in multiple pathways governing the levels of CLB and N-CLB.

- 2. As part of population PK analysis for effects of ethnicity, we recommend that you include Caucasians, Blacks, Hispanics, and Asians representing the population in US. For 2C19 genotyping, we recommend that *2,3 and preferably also *4-6 for Caucasian be studied.**

Meeting Discussion:

- The Sponsor stated that the *in vitro* investigation for protein-binding of N-CLB is ongoing.
- In response to the Agency's recommendation for an *in vivo* drug-drug interaction study for CYP2C9 inhibition, the Sponsor expressed that the population analysis approach will be used to address the potential impact of N-CLB on CYP2C9 activity by pooling data of concomitant valproic acid (substrate of CYP2C9) in approximately 60 subjects taking different doses of CLB.
- The Sponsor agreed to the Agency's recommendations for P-gp evaluations, highest ketoconazole dose, and CYP2C19 genotyping.
- The Sponsor presented the metabolic pathways for CLB (same as that in briefing package) and expressed that the impact of CYP2C19 will be evaluated through population analysis in Phase 3 study. The Sponsor expressed that the concomitant topiramate, a CYP2C19 inhibitor, will yield pertinent information for population analysis. In addition, concomitant felbamate, a CYP3A4 inducer and CYP2C19 inhibitor, should provide further information to address the Agency's concern for exposure of CLB and N-CLB as a result of CYP2C19 inhibition. The Agency pointed out that both topiramate and felbamate are not considered as potent CYP2C19 inhibitors recommended for the investigation. In addition, the mixed effect of concomitant felbamate, instead of a potent inhibitor of CYP2C19, on exposure of parent drug CLB through its effect on multiple enzymes in multiple pathways may not provide the clarity to address the Agency's concern. The Sponsor expressed that felbamate has CYP2C19 inhibition potency close to omeprazole and will provide justifications, along with results of population analysis, in the future.

FDA Post-Meeting Follow-up Comments:

We do not believe that population PK analysis on valproic acid data is the best approach to evaluate the potential drug-drug interaction via CYP2C9 inhibition and the results may be inconclusive, for the following reasons:

- The involvement of multiple metabolic enzymes (e.g., CYP2C19, CYP2C9, and UGT) for valproic acid
- The potential for valproic acid to inhibit the activity of CYP2C9 (as reported in literature)
- The lack of impact on PK of valproic acid does not eliminate the potential of CYP2C9 inhibition by N-CLB for concomitant medications that are more sensitive CYP2C9 substrates more exclusively metabolized by CYP2C9.
- To maximize the inhibition potential as the worst case scenario for safety and for labeling purpose (i.e., potential dosage adjustment), one should evaluate a sensitive substrate of CYP2C9.

Therefore, the Sponsor should use a sensitive probe substrate (e.g., warfarin, phenytoin) for an in vivo study, unless such comedications are included in proposed clinical trials to allow evaluation through population analysis.

Question 7b: Does the Division agree that, together with the studies presented in the IND, all available literature studies, results from the Phase II clinical study and consequent population PK analysis, the planned in vivo drug interaction study with ketoconazole (inhibition), and the rigorous population PK plan in the planned Phase III study are adequate for NDA submission and adequately provide labeling information and guidance for clinicians treating patients with LGS?

FDA Preliminary Response:

Clinical Pharmacology

The proposal is acceptable. Based on known pharmacokinetics of clobazam and its active metabolite, you have proposed to collect plasma samples at pre-dose and within time windows of 1-2, 2-4 and 4-8 hours post-dose at steady state during the maintenance period of Weeks 5 to 11 of clobazam treatment. In addition, a full PK profile will also be collected from Phase-I studies. There will be adequate information to characterize the PK of clobazam and its active metabolite.

Meeting Discussion:

It was recommended that the Sponsor collect information on dose, duration of treatment with concomitant medications that will be evaluated for pharmacokinetic interactions as a part of a population pharmacokinetic analysis.

Question 8: Appropriate language for the product labeling of drugs that are cleared hepatically is outlined in FDA's guidance for industry. Does the Division agree that clobazam administration to hepatically-impaired patients has been adequately characterized in the literature study summarized below?

FDA Preliminary Response:

Clinical Pharmacology

Although it seems reasonable, this will ultimately be a review issue at the NDA stage, and you should provide a more comprehensive summary and justification at the time of submission.

Meeting Discussion:

There was no further discussion of this question at the meeting.

PK/PD

Question 9: Does the Division agree that the food-effect studies conducted to date and available as literature publications are adequate for NDA submission?

FDA Preliminary Response:

Clinical Pharmacology

The food effect studies in literature publications that you cite appear to use different formulations (e.g., capsules). Therefore, it will be necessary to conduct a food effect study to evaluate the impact of food on the proposed commercial formulation, unless a food effect study was conducted on the Phase 2 formulation (which will be linked to the commercial formulation through a BE study).

Meeting Discussion:

The Sponsor agreed and stated that an additional arm has been added to the proposed BE study to evaluate the effects of food using the highest tablet strength of clobazam.

Question 10: Does the Division agree that the alcohol effect studies described below and available as literature publications along with proposed labeling similar for the class of benzodiazepines are adequate for NDA submission?

FDA Preliminary Response:

The alcohol effect studies and the proposed labeling are sufficient.

Meeting Discussion:

There was no further discussion of this question at the meeting.

NONCLINICAL

Question 11: Does the Division agree with the completed, ongoing and planned toxicology studies as being adequate to support Phase III development and registration?

FDA Preliminary Response:

The adequacy of the studies will be a matter of review. You will need to provide data on plasma exposure to the parent compound and major circulating metabolites at the doses used in the pivotal nonclinical studies. It will be important to show that the major human metabolites (e.g., N-CLB) have been adequately assessed in the nonclinical studies. Because of the high circulating levels of N-CLB in humans, this metabolite should be tested directly in the standard genetic toxicology battery (cf. Guidance for Industry S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals July 1997 ICH).

Meeting Discussion:

The Sponsor agreed to conduct genotoxicity studies of the metabolite, N-CLB, alone.

Question 12: Does the Division agree with Ovation's proposed nonclinical plans along with rigorous cardiac safety monitoring in the Phase III study to provide an integrated risk assessment of the cardiac safety profile of clobazam?

FDA Preliminary Response:

Yes, from a nonclinical standpoint.

Meeting Discussion:

The Agency stated that, in addition to cardiac monitoring in the Phase 3 study, a QT study would be required to complete the risk assessment of the cardiac safety profile. The Agency also recommended that the sponsor quantify the relationship between concentration-QT analysis using a mixed-effects modeling approach.

CHEMISTRY, MANUFACTURING AND CONTROLS

Question 13: Does the Division concur with Ovation's plan for a relative bioavailability study at the highest tablet strength of 20 mg and that biowaivers can be requested for lower dosage strengths given scaleable compositions and similar dissolution profiles?

FDA Preliminary Response:

Clinical Pharmacology

Yes, from a clinical pharmacology perspective, if you can demonstrate similarity in composition and in dissolution profiles in at least 3 different media for various proposed strengths.

Meeting Discussion:

The Sponsor agreed and there was no further discussion of this question at the meeting.

Question 14: Does the Division agree that the planned BE study comparing the Phase II tablet formulation versus the Phase III tablet formulation is adequate to support the formulation change and support NDA approval of the formulation to be used in the Phase 3 clinical study?

FDA Preliminary Response:

Clinical Pharmacology

Yes, from a clinical pharmacology perspective.

Meeting Discussion:

There was no further discussion of this question at the meeting.

PEDIATRIC WAIVER AND LABELING

Question 15: Does the Division agree to grant a waiver from studying patients with LGS <2 years of age if PREA is applicable? Please note Ovation intends to seek Orphan Designation for this product which would exempt Ovation from PREA requirements.

FDA Preliminary Response:

Orphan Designation would exempt clobazam from the PREA requirement.

If PREA is applicable, the lower age limit would correspond to the lower age limit for Lennox-Gastaut (1 year of age according to the ILAE classification).

Meeting Discussion:

The Sponsor agreed with the Agency's preliminary response, and there was no further discussion of this question at the meeting.

Question 16: Does the Division agree that the planned crushed-tablet BA study will support pediatric dosing and administration recommendations in the product label for the NDA?

FDA Preliminary Response:

Clinical Pharmacology

If pediatric data are generated in clinical trials, the planned crushed-tablet BA study should generally be sufficient to provide dosing and administration recommendations. However, if you plan to administer the drug as crushed tablet in apple sauce in the phase 3 trial, the relative BA study (crushed tablet in apple sauce vs. intact tablet) should be conducted prior to the initiation of Phase 3 trial for supporting the dosing in Phase 3 clinical trial.

Meeting Discussion:

The Sponsor agreed with the Agency's preliminary response. The Agency stated that the Sponsor should bridge the dosage forms of administering clobazam as an intact capsule vs. crushing clobazam in applesauce for administration. In case there are differences in bioavailability due to administration with applesauce, the Sponsor should conduct simulations to propose an alternate dose that would match the drug exposure.

ABUSE LIABILITY

Question 17: Clobazam is a 1,5 benzodiazepine and has been scheduled by the DEA as Schedule IV since 1984 (49 FR 39307, 1984) in accordance with the substance's identification as Schedule IV by the UN Convention on Psychotropic Substances. Clobazam shares many pharmacological properties with other members of the benzodiazepine class of drugs, including the potential for physiological drug dependence. Does the Agency agree that a formal abuse liability assessment (8 Factor Analysis) is not required to support the planned NDA?

FDA Preliminary Response:

Controlled Substance Staff (CSS)

1. *Clobazam is a marketed drug in other countries and is already Schedule IV internationally. Thus, it is also a Schedule IV substance in the U.S. under the Controlled Substances Act (CSA). During our review, we will focus on primary data from clinical efficacy/safety studies that you conduct regarding psychiatric and neurological adverse events, prospective clinical studies on physical dependence and tolerance, and on epidemiological data, if available.*
2. *A human abuse liability study will not need to be conducted with clobazam to retain the substance in Schedule IV of the CSA.*
3. *During our review, we will consider currently approved doses of clobazam in other countries as compared to the therapeutic dose(s) of clobazam chosen for marketing in the U.S.*
4. *Primary data from abuse-related preclinical and clinical studies should be submitted in the NDA. Study summaries (including published papers) are inadequate for review purposes.*
5. *According to 21 CFR § 314.50 (5) (vii), the Abuse Potential Section of an NDA includes the following:*

-- Proposal for scheduling and all scientific data supporting the proposal

-- The Abuse Potential Assessment includes the following:

- *Chemistry (including chemical similarity to other drugs of abuse and ability to extract the drug of abuse from the preparation)*
- *Pharmacokinetics and pharmacodynamics (including full data on receptor binding)*
- *Primary data from abuse potential studies in animals and humans*

- *Adverse events in clinical studies related to abuse potential*
 - *Integrated summaries of safety and efficacy (ISS and ISE)*
 - *Information related to overdose*
 - *Prospective assessment of the incidence of misuse, abuse, physical dependence/withdrawal syndrome, tolerance, diversion during clinical studies*
6. *Data from the studies listed above (if available) will form the basis of the Drug Abuse and Dependence section of the product label.*
7. *An 8 Factor Analysis is a document that is prepared by the Agency (on behalf of the Department of Health and Human Services) that considers the medical and scientific evidence to determine whether a substance should be recommended for scheduling by the Drug Enforcement Administration. Thus, you would not prepare an 8 Factor Analysis.*

Meeting Discussion:

For preliminary response #4, the Sponsor stated that they did not have formal abuse liability studies. The Agency responded that formal abuse liability studies would not need to be submitted if the Sponsor accepted the standard language regarding abuse for benzodiazepines.

GENERAL CLINICAL PHARMACOLOGY COMMENTS:

FDA Preliminary Response:

The need for a study in renal impairment should be based on a thorough understanding of the results of human mass-balance study and the activity of the metabolites (and hence contribution of the active species). You need to also clarify whether M9 is renally excreted (there is a discrepancy in the package, in one place it says it is renally excreted, and in another place it is not).

Meeting Discussion:

As discussed for Question #6, the Sponsor will provide clarification, more details, and justification.

Summary and Action Items

The Sponsor will consider the Division's advice above.

Minutes Preparer:

Tamy Kim, PharmD
Regulatory Project Manager, Division of Neurology Products

Chair Concurrence:

Russell Katz, MD
Director, Division of Neurology Products

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/s/

Russell Katz
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MEMORANDUM OF MEETING MINUTES

Meeting Date: October 13, 2004
Application: Pre IND 70,125; Clobazam
Indication: Lennox-Gastaut Syndrome
Type of Meeting: PreIND
Meeting Chair: Russell Katz, M.D.
Meeting Recorder: Jacqueline Ware, Pharm.D.

FDA Attendees:

David Claffey,	Chemistry Reviewer, Division of Neuropharmacological Drug Products (DNDP)
John Feeney, M.D.	Neurology Team Leader, DNDP
Ed Fisher, Ph.D.	Pharmacology Reviewer, DNDP
Lois Freed, Ph.D.	Supervisory Pharmacologist, DNDP
Martha Heimann, Ph.D.	Acting Chemistry Team Leader, DNDP
Russell Katz, M.D.	Director, DNDP
Ronald Kavanagh, Ph.D.	Reviewer, Office of Clinical Pharmacology and Biopharmaceutics (OCPB)
Paul Maher, M.D.	Medical Officer, Office of Orphan Products Development
Phil Sheridan, M.D.	Medical Officer, DNDP
Sally Yasuda, Ph.D.	Acting Team Leader, OCPB
Jackie Ware, Pharm.D.	Regulatory Project Manager, DNDP

Ovation Pharmaceuticals, Inc.

Sponsor Attendees:

Holli Carlson	Director, Clinical Affairs - Operations
Stephen Collins, M.D., Ph.D.	Chief Scientific Officer and Vice President, Clinical Affairs
Patricia Frank, Ph.D.	Consultant, Preclinical
Ben Quintana, Ph.D.	Director, Manufacturing Development
Mike Rice, Ph.D.	Vice President, Manufacturing Development and Quality Assurance
Bill Riley	Clinical Project Manager
Tom Stothoff	Associate Director, Regulatory Affairs
Jenny Swalec	Associate Director, Regulatory Affairs
Katherine Tracy, M.D., Ph.D.	Vice President, Clinical Research

This was a Pre-IND meeting to discuss Ovation's upcoming IND submission and clinical development program for Clobazam in the treatment of patients with Lennox-Gastaut Syndrome.

Discussion Points: Below are the sponsor's questions with the FDA responses. The Biopharmaceutics section contains comments that may not have been discussed at the meeting.

(For full questions, please see briefing package).

REGULATORY

- For the initial Clobazam IND for the treatment of patients with LGS, Ovation is proposing to submit the following information (see Table 2). Does FDA concur?

- For the IND, there appears to be enough previous experience to potentially support the study as proposed. The sponsor should summarize the previous clinical safety experience.
- More information is needed on pharmacokinetics, route of metabolism, and drug interactions. Pediatric pharmacokinetics should be studied down to 2 years of age. *Please see Biopharm section below for more specific comments.*
- The sponsor must make the case that prior experience at these doses in kids, with these concurrent medications, support the case that the proposed study is safe.
- The Division suggested exploring more doses or explaining the rationale behind dose selection in the IND.
- The Division questioned whether animals were exposed to the same circulating moieties as humans. The IND should make a case to answer the question in a quantitative way.
- The ability of young children to [REDACTED] (b) (4) was discussed. Ovation will re-evaluate this issue if the study population is expanded to include children down to 2 years of age.

BIOPHARMACEUTICS, PHARMACOKINETICS, AND CLINICAL PHARMACOLOGY

- As a new chemical entity in the US the sponsor will need to submit a complete clinical pharmacology section, including full study reports and bioanalytic information for the NDA. In addition, the type and quality of the information submitted needs to be up to present standards. Published literature may be submitted. However the sponsor should be aware that lack of analytic information and poor quality of study designs often means that literature submitted from public sources is frequently not adequate.
- For the IND, summary information might be acceptable. However due to the age of the drug and to insure that the information that is needed is actually included in the submission the sponsor is advised that submission of copies of publications and study reports are recommended.

Phase II Dose Ranging Study

- The age range of 3 – 30 years old proposed for the phase II dose ranging study may not cover the appropriate pediatric age range. Texts indicate seizure onset from age 0 – 3 years when pharmacokinetics may be changing rapidly, with onset of Lennox-Gastaut Syndrome typically at 2 years of age.
- The plans for population pharmacokinetic sampling are insufficient to assess their adequacy for providing information for guiding dosing. In addition, the baseline pharmacokinetic information that would be needed prior to population PK studies with sparse sampling appears to be inadequate.

- There is no indication that patients will be stratified by age or gender. If patients are not stratified by age then the study population might not contain adequate numbers of subjects throughout the age range for appropriate pharmacokinetic analyses needed to guide dosing for phase III at various ages. Gender stratification, combined with information regarding age and sexual maturity will be particularly useful for selecting dosages in pubescents, teenagers and adults.
- There may not be adequate subjects in this study to adequately describe true differences in a number of other factors, such as treatment as either monotherapy or adjunctive therapy. Specifically in the face of the variety of concomitant medication regimens that patients will likely be receiving and the likelihood of complex drug-drug interactions, including both pharmacokinetic and pharmacodynamic drug interactions, it is highly probable that population pharmacokinetic modeling will not be adequate by itself to provide adequate information to guide dosing for phase III studies without additional *in vivo* drug-drug interaction studies. *In vivo* metabolic drug-drug interaction studies should be guided by mass balance information and *in vitro* drug metabolism.
- Based upon recently published information, it may be useful to genotype subjects for CYP2C19. [DRUG METABOLISM AND DISPOSITION, 2004; Vol. 32, No. 11: 1279–1286]
- Additional consultations with OCPB regarding pharmacometrics are available if needed.
- The sponsor indicated during the meeting that they are obtaining guidance from (b) (4)

Other Comments

Submission Quality

- The pharmacokinetic information that was submitted was inconsistent between different parts of the submission, e.g. with respect to metabolite pharmacokinetics.

Dosage

- The lowest weight to be allowed in the proposed study is 12.5 kg which is at 50th percentile for 3 yo males and between the 50th and 75th percentiles for females. Patients with Lennox-Gastaut Syndrome are expected to have a higher fraction of individuals with low weights for their age and subjects at the lowest ages when pharmacokinetics may be changing most rapidly would be inappropriately excluded. Thus in practice the youngest patients with Lennox-Gastaut Syndrome might have excessive drug exposures.

- (b) (4)

If the sponsor anticipates that a range of dosages may be needed for labeling purposes, such as 0.5 – 1.0 mg/kg, then a dose response trial that includes the anticipated range along with a likely ineffective dose may be appropriate.

Formulation

- A non-solid formulation may be needed for pediatric patients for both dosage adjustment and the ability to administer the drug orally.

- In response to this comment, during the meeting the sponsor indicated that due to the (b) (4) and based upon discussions with pediatric neurologists they believe (b) (4)
- The sponsor indicated during the meeting that they were uncertain if the proposed (b) (4)
- (Post meeting note – stability in applesauce, bioavailability, and demonstration that the administration method proposed is feasible in the intended population will need to be addressed or supported if this method of administration is used or recommended.)

From the perspective of Clinical Pharmacology and Biopharmaceutics based on the available information the following issues also need clarification and might aid in the design of phase III studies, for labeling, or regulatory requirements.

Bioavailability

- Bioavailability relative to an optimally available oral formulation is a regulatory requirement per the Code of Federal Regulations.
- Food effects will need to be examined, both a high-fat, high-caloric meal and the effect of administration in applesauce if this method of administration is used.

Metabolism

- The influence and kinetics of active metabolites are of particular interest. It's notable that the N-desmethyl metabolite is claimed to be approximately half to equipotent to the parent compound. In addition, the possible activity of other metabolites is of interest.
- Literature information available prior to the meeting indicates that time invariance may occur, and that the time to reach steady-state for both parent and active metabolites may be as long as 1 month. This has implications for dosage adjustments as measurement of therapeutic effect may not be appropriate until after steady-state has been achieved. Premature assessments of drug effects and premature upward titration can result in excessive toxicity and inaccurate assessments of the therapeutic index.
- Results of mass balance studies should be provided to assess the metabolic profile of clobazam along with the exposure to and formation clearances of metabolites. The activity of any metabolites and their contribution to effect should also be assessed and any impact on dosage adjustments should be addressed. Mass balance studies will also provide guidance with respect to *in vitro* studies needed. During the meeting the sponsor indicated that clobazam is a CYP 2C19 inhibitor and metabolism of clobazam is inhibited by CYP3A4 inhibitors. Interactions of glucuronidation such as with lamotrigine have not been assessed.

- The sponsor indicated that they are obtaining guidance from (b) (4)

Drug Interactions

- In addition to metabolic drug interactions, pharmacodynamic drug interactions, (e.g. EEG), and the effect of alcohol on absorption should be addressed in order to provide guidance for dosage adjustments.

Other Dosing Issues

- Kinetics and dosing in special populations should be addressed, i.e. renal and hepatic insufficiency.
- The frequency and timing of dosing should be considered and justified. For example due to the expected CNS depression and long half-life qhs administration may be sufficient.
- Tolerance to the effect of benzodiazepines has been described in this population with recovery of efficacy following a drug holiday. This should be addressed along with the possibility that disease progression may alter efficacy or dosing over time. The latter may have implications for assessing dose response using a heterogeneous population who have had the syndrome for varying durations. Severity of the syndrome may also be a factor for dosing.

Pharmacodynamics

- The sponsor indicated during the meeting that clobazam may have less muscle relaxing properties than other benzodiazepines. Thus information on binding at GABA receptors for clobazam and its metabolites may be useful to the sponsor in assessing therapeutic index at various dosages especially relative to other benzodiazepines. (This information is not being requested by OCPB but is only for the sponsor's consideration).

Potential for QT Prolongation (Post Meeting Note)

- The sponsor should address the potential for QT prolongation according to present standards. The sponsor is referred to FDA draft guidances.

PRECLINICAL

- In light of the clinical experience with Clobazam, does the FDA concur that the available toxicology package is sufficient?
 - **The Division agreed that the available nonclinical data are sufficient to support the proposed clinical trial. However, the following additional data need to be submitted:**

(a) a full battery of genotoxicity studies (i.e., an *in vitro* test for gene mutation in bacteria, either an *in vitro* clastogenicity assay in mammalian cells or an *in vitro* mouse lymphoma tk assay (with colony sizing), and an *in vivo* micronucleus assay in rodent (cf . Guidance for Industry: S2B Genotoxicity: A Standard Battery for Genotoxicity Testing of Pharmaceuticals. ICH July 1997). These studies should be submitted as soon as possible.

(b) a juvenile study in rats. The sponsor may submit a study protocol for review and feedback by the Division.

(c) toxicokinetic (TK) data in the animal species used for the definitive toxicology studies (including general and reproductive toxicology and carcinogenicity). It is the Division's understanding that TK data were not collected in these studies. If this is correct, then the sponsor would need to conduct additional studies using the same doses and dosing regimen used in the definitive studies in order to collect plasma exposure data for parent compound and major metabolites. These bridging studies need to be of a duration sufficient to ensure that steady state has been achieved, and to adequately characterize any changes in kinetics (e.g., enzyme induction, inhibition) with multiple dosing. These data should be submitted as soon as possible.

- The Division requested that the safety pharmacology studies be submitted. While full study reports are preferred, a detailed summary of the data would be sufficient.
- With the exception of these genotoxicity studies, does the FDA agree that the necessary carcinogenicity evaluation has been completed?
 - The sponsor has conducted oral carcinogenicity studies in mouse (80-week) and rat (104-week). On face, these studies address the need for evaluation of carcinogenicity potential. However, the adequacy of these studies will be a matter for review. For each study not conducted according to Good Laboratory Practices (GLP), a list of all deviations from GLP needs to be provided, with a discussion of how the deviations impact on the interpretation of the study.

CLINICAL

- Does the FDA agree that the proposed Phase 2 clinical trial is acceptable given the clinical data and information that exists for Clobazam?
 - Yes, but some concerns have already been discussed above.

CMC

- Does the FDA concur with the CMC stability proposals?

- **The Division concurs. However, the sponsor will need to ensure that the levels of “Other” related substances (NMT ^{(b) (4)}), have been qualified, and that they are listed individually according to HPLC retention time.**
- We are seeking FDA’s agreement that this level of analytical control is appropriate for the conduct of clinical trials in the U.S.
 - **The Agency concurs with this level of analytical support. The related substances specified levels are all within the ICH guideline levels (0.5%).**

ORPHAN DRUG PRODUCTS

- **Since this drug is approved elsewhere for the broad indication of epilepsy, the sponsor must make the case for Orphan Designation**
 - **Show that Lennox-Gastaut Syndrome is a valid subset of general epilepsy.**
 - **Explain why the drug is different from other agents.**

Minutes Preparer: _____
Courtney Calder, Pharm.D.

Chair Concurrence: _____
Russell Katz, M.D.

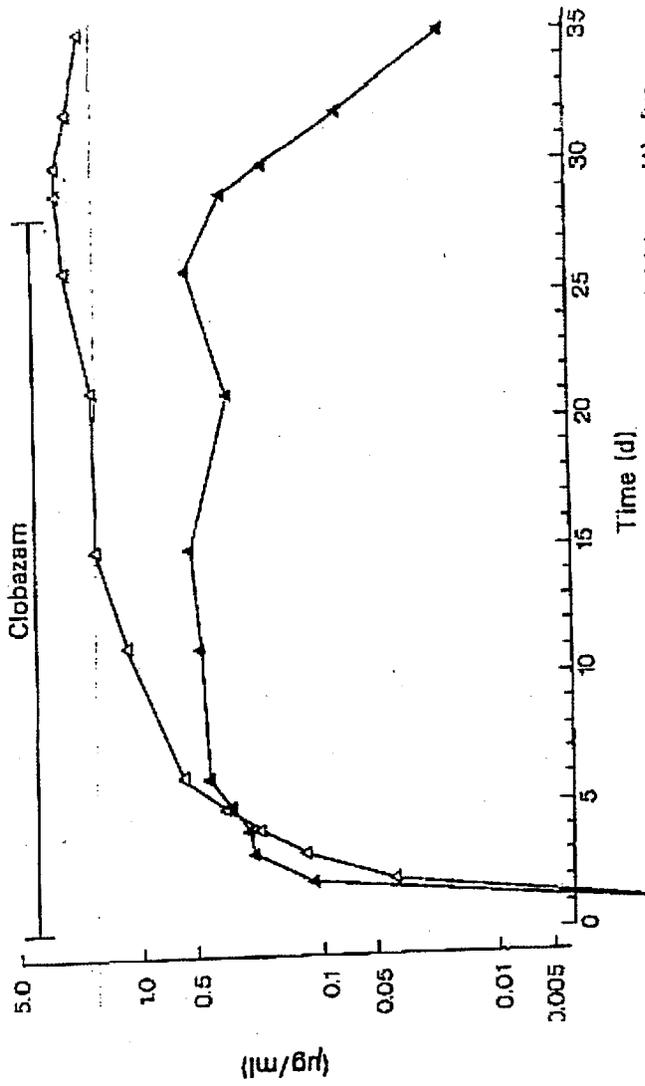


Figure 8 Minimum serum levels of unchanged clobazam (▲) and N-desmethyloclobazam (Δ) after clobazam 10 mg twice daily for 28 days. Means of ten subjects. GLC assay method.

PK: Parent/Active Metabolite

	Clobazam	Nor-Clobazam	Reference
t _{1/2} (hr)	18 (10-30)	42 (36-46)	Aucamp
t _{1/2} (hr)	N/A (0-55)	60 (35-133)	Engle
t _{1/2} (hr)	adult 12 (SD 6)	49 (SD 38)	Bun
t _{1/2} (hr)	peds 16 (SD 3)	15 (SD 2)	Bun
C _{SS} ratio CLB:NorCLB	1	8x	Rupp
C _{SS} ratio CLB:NorCLB	1	~10x	Guberman

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this page is the manifestation of the electronic signature.**

/s/

Russell Katz
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